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Hiroyuki [JP/JP]; 11-1, Miyanokawahara 1-chome, Takatsuki-shi, Osaka 569-1032 (JP). YAMANE, Tahei [JP/JP]; 10-6-203, Tsukimigaoka, Nigawa, Takarazuka-shi, Hyogo 665-0067 (JP).

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(74) Agent: TAKASHIMA, Hajime; Fujimura Yamato Seimei Bldg., 2-14, Fushimimachi 4-chome, Chuo-ku, Osaka-shi, Osaka 541-0044 (JP).

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(71) Applicant (for all designated States except US): TAKEDA CHEMICAL INDUSTRIES, LTD. [JP/JP]; 1-1, Doshomachi 4-chome, Chuo-ku, Osaka-shi, Osaka 541-0045 (JP).

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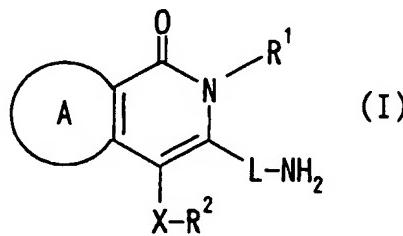
(72) Inventors; and

(75) Inventors/Applicants (for US only): OI, Satoru [JP/JP]; 7-10-509, Ayameikeminami 1-chome, Nara-shi, Nara 631-0033 (JP). IKEDOU, Koji [JP/JP]; 6-4, Besshochokobayashi, Himeji-shi, Hyogo 671-0222 (JP). TAKEUCHI, Koji [JP/JP]; 50-B-204, Yamadaminami, Suita-shi, Osaka 565-0823 (JP). OGINO, Masaki [JP/JP]; 15-13, Kamino-cho, Nishinomiya-shi, Hyogo 663-8021 (JP). BANNO, Yoshihiro [JP/JP]; 17-17-202, Meishincho, Takatsuki-shi, Osaka 569-1128 (JP). TAWADA,

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(54) Title: FUSED HETEROCYCLIC COMPOUNDS

(57) Abstract: The present invention provides a compound of the formula: wherein ring A is an optionally substituted 5 to 10-membered aromatic ring; R¹ and R² are the same or different and each is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group; X is a bond and the like; and L is a divalent hydrocarbon group, and a salt thereof, except 3-(aminomethyl)-2,6,7-trimethyl-4-phenyl-1(2H)-isoquinolinone, 3-(aminomethyl)-2-methyl-4-phenyl-1(2H)-isoquinolinone, 3-(aminomethyl)-6-chloro-2-methyl-4-phenyl-1(2H)-isoquinolinone and 3-(aminomethyl)-2-isopropyl-4-phenyl-1(2H)-isoquinolinone. The compound shows a superior peptidase-inhibitory activity and is useful as an agent for the prophylaxis or treatment of diabetes and the like.

DESCRIPTION
FUSED HETEROCYCLIC COMPOUNDS
TECHNICAL FIELD

The present invention relates to a novel fused heterocyclic compound having a peptidase (preferably dipeptidyl dipeptidase IV) inhibitory activity, which is useful as a prophylactic or therapeutic agent of diabetes and the like.

BACKGROUND ART

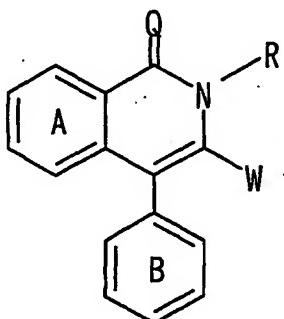
Peptidase is known to relate to various diseases. Dipeptidyl dipeptidase IV (hereinafter sometimes to be abbreviated as DPP-IV), which is one kind of peptidases, is serine protease that specifically binds with a peptide containing proline (or alanine) at the 2nd from the N terminal and cleaves the C-terminal side of the proline (or alanine) to produce dipeptide. DPP-IV has been shown to be the same molecule as CD26, and reported to be also involved in the immune system. While the role of DPP-IV in mammals has not been entirely clarified, it is considered to play an important role in the metabolism of neuropeptides, activation of T cells, adhesion of cancerous cells to endothelial cells, invasion of HIV into cells and the like. Particularly, from the aspect of glycometabolism, DPP-IV is involved in the inactivation of GLP-1 (glucagon-like peptide-1) and GIP (Gastric inhibitory peptide/Glucose-dependent insulinotropic peptide), which are incretins. With regard to GLP-1, moreover, its half-life in plasma is as short as 1-2 minutes, and GLP-1 is known to be degraded by DPP-IV and markedly lose its physiological activity because GLP-1(9-36)amide, which is a degradation product by DPP-IV, acts on GLP-1 receptor as an antagonist. It is also known that suppression of degradation of GLP-1 by inhibiting activity of DPP-IV leads to potentiation of physiological activity that GLP-1 shows, such as glucose concentration-dependent insulinotropic effect.

and the like. From these facts, a compound having a DPP-IV inhibitory activity is expected to show effect on impaired glucose tolerance, postprandial hyperglycemia and fasting hyperglycemia observed in type I and type II diabetes and the like, , obesity or diabetic complications associated therewith and the like.

As therapeutic agents of diabetes now in use, a sulfonylurea, a biguanide, an α -glucosidase inhibitor and the like are known. While a sulfonylurea produce a potent hypoglycemic action, it sometimes causes serious hypoglycemia and requires attention during use. A biguanide easily causes lactic acidosis which is a relatively serious side effect. An α -glucosidase inhibitor delays digestion and absorption of glucose in the gastrointestinal tract and suppresses increase in the blood glucose level after meal, but side effects of sense of distension, diarrhea and the like are problematic (JOSLIN'S DIABETES MELLITUS 13Th Edition 521-522).

Isoquinolone compounds are described in the following publications.

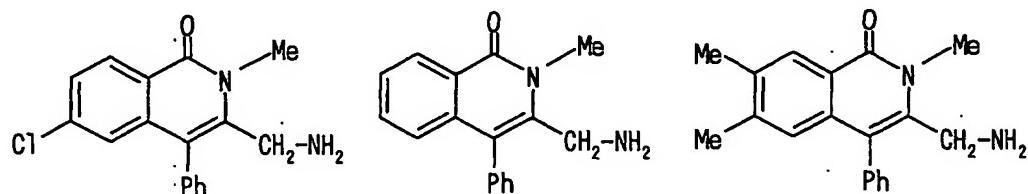
(1) JP-A-7-76573 describes a compound of the formula



wherein ring A and ring B are optionally substituted benzene rings; Q is an oxygen atom or a sulfur atom; R is a hydrogen atom, an optionally substituted hydrocarbon group and the like; W is $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{NHR}^1$, -

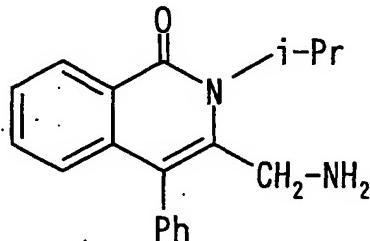
$\text{CH}_2\text{CH}_2\text{NHR}^1$ (R^1 is hydrogen atom or optionally substituted hydrocarbon group) and the like, as a starting material compound of a compound having a calcium antagonistic action and the like, wherein the specific examples are

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(2) Archiv der Pharmazie, vol. 324, pp. 809-814 (1991) describes a compound of the formula

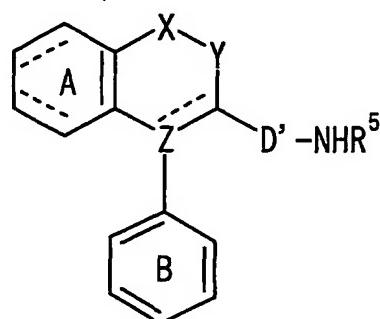
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as a starting material compound of a compound having an anticonvulsant action.

(3) JP-A-7-10844 describes a compound of the formula

15



wherein ring A is optionally substituted; ring B is an optionally substituted benzene ring; one of X and Y is -

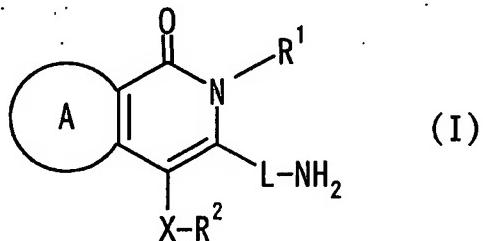
NR¹⁻ (R¹ is a hydrogen atom, an optionally substituted hydrocarbon group and the like), -O- or -S-, the other is -CO-, -CS- and the like; ---- is a single bond or a double bond; Z is a carbon atom and the like; D' is a C₁-₅ alkylene group; and R⁵ is a hydrogen atom or an optionally substituted hydrocarbon group] as a starting material compound of a compound having an acyl-CoA cholesterol acyl transferase (ACAT) inhibitory action and the like.

10 However, there is no report showing that these compounds have a peptidase (preferably DPP-IV) inhibitory activity.

15 There is a demand on the development of a compound having a peptidase (preferably DPP-IV) inhibitory activity, useful as a prophylactic or therapeutic drug of diabetes and the like and having superior properties in terms of efficacy, duration of action, specificity, low toxicity and the like.

SUMMARY OF THE INVENTION

20 The present inventors have first found that a compound of the formula



wherein

ring A is an optionally substituted 5 to 10-membered aromatic ring;

25 R¹ and R² are the same or different and each is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;

30 X is a bond, -O-, -S-, -SO-, -SO₂- or -NR³⁻

(R³ is a hydrogen atom or an optionally substituted hydrocarbon group); and L is a divalent hydrocarbon group, and a salt thereof,

5 which are characterized by the chemical structure where an amino group is bonded to a fused heterocycle via a divalent hydrocarbon group, have a superior peptidase (preferably DPP-IV) inhibitory activity and are useful as a prophylactic or therapeutic

10 agent of diabetes and the like. Based on this finding, the present inventors have conducted intensive studies and completed the present invention.

Accordingly, the present invention relates to:

- 1) a compound of the formula (I) or a salt thereof
- 15 except 3-(aminomethyl)-2,6,7-trimethyl-4-phenyl-1(2H)-isoquinolinone, 3-(aminomethyl)-2-methyl-4-phenyl-1(2H)-isoquinolinone, 3-(aminomethyl)-6-chloro-2-methyl-4-phenyl-1(2H)-isoquinolinone and 3-(aminomethyl)-2-isopropyl-4-phenyl-1(2H)-isoquinolinone,
- 20 2) the compound of 1), wherein the 5 to 10-membered aromatic ring for ring A is a benzene ring;
- 3) the compound of 1), wherein the ring A is a 5 to 10-membered aromatic ring optionally having 1 to 3 substituent(s) selected from
- 25 a) a halogen atom,
- b) a nitro group,
- c) a cyano group,
- d) a C₁₋₃ alkyleneoxy group,
- e) a C₁₋₁₀ alkyl group or a C₂₋₁₀ alkenyl group, each
- 30 optionally having 1 to 3 substituent(s) selected from a halogen atom, a hydroxy group, a carboxyl group, an alkoxy carbonyl group having 2 to 8 carbon atoms, a carbamoyl group, a cyano group, an amino group, an alkanoylamino group having 2 to 8 carbon atoms, an
- 35 alkoxy carbonylamino group having 2 to 8 carbon atoms, an alkylsulfonylamino group having 1 to 8 carbon atoms,

- f) an optionally substituted hydroxy group,
- g) an acyl group,
- h) an optionally substituted amino group,
- i) an aryl group having 6 to 14 carbon atoms,
- 5 j) an optionally substituted thiol group, and
- k) an optionally substituted heterocyclic group,
- 4) the compound of 1), wherein R¹ is an alkyl group having 1 to 10 carbon atom(s),
- 5) the compound of 1), wherein R¹ is an alkyl group having 4 to 10 carbon atoms,
- 10 6) the compound of 1), wherein X is a bond or -O-,
- 7) the compound of 1), wherein the divalent hydrocarbon group for L is an alkylene group having 1 to 10 carbon atom(s),
- 15 8) the compound of 1), wherein R² is an optionally substituted hydrocarbon group,
- 9) the compound of 1), wherein R² is an alkyl group having 1 to 10 carbon atom(s), an aryl group having 6 to 14 carbon atoms or an aralkyl group having 7 to 13
- 20 carbon atoms, each optionally having 1 to 3 substituent(s) selected from halogen atom, hydroxy group, nitro group, amino group, optionally halogenated alkyl group having 1 to 6 carbon atom(s), alkoxy group having 1 to 6 carbon atom(s), aromatic heterocyclic group and
- 25 cycloalkyl group having 3 to 10 carbon atoms,
- 10) the compound of 1), which is 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-1,3-thiazole-4-carbonitrile,
- 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-
- 30 dihydro-6-isoquinolyl]-1,3-thiazole-4-carboxylic acid,
- 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-1,3-thiazole-4-carboxamide,
- ethyl 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-1,3-thiazole-4-carboxylate,
- 35 (E)-3-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-2-propenamide,

- (E)-3-[3-(aminomethyl)-2-isobutyl-4-phenyl-1-oxo-1,2-dihydro-6-isoquinolyl]-2-propenamide,
3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinecarboxamide,
- 5 2-[[3-(aminomethyl)-2-isobutyl-4-phenyl-1-oxo-1,2-dihydro-6-isoquinolyl]oxy]acetamide,
or a salt thereof,
- 11) a crystal of 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-1,3-thiazole-4-
- 10 carbonitrile or a salt thereof,
- 12) a crystal of 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-1,3-thiazole-4-carboxamide or a salt thereof,
- 13) a crystal of 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-1,3-thiazole-4-
- 15 carboxamide or a salt thereof,
- 14) a crystal of ethyl 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-1,3-thiazole-4-carboxylate or a salt thereof,
- 20 15) a crystal of (E)-3-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-2-propenamide or a salt thereof,
- 16) a crystal of (E)-3-[3-(aminomethyl)-2-isobutyl-4-phenyl-1-oxo-1,2-dihydro-6-isoquinolyl]-2-propenamide or
- 25 a salt thereof,
- 17) a crystal of 3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinecarboxamide or a salt thereof,
- 18) a crystal of 2-[[3-(aminomethyl)-2-isobutyl-4-phenyl-1-oxo-1,2-dihydro-6-isoquinolyl]oxy]acetamide or
- 30 a salt thereof,
- 19) a pharmaceutical agent containing a compound of the formula (I) or a salt thereof,
- 20) a pharmaceutical agent comprising the pharmaceutical agent of 19) above in combination with at least one
- 35 member selected from an insulin preparation, an insulin

sensitizer, an α -glucosidase inhibitor, a biguanide and an insulin secretagogue,

21) an agent for prophylaxis or treatment of diabetes, which contains a compound of the formula (I), a salt thereof or a prodrug thereof,

22) an agent for prophylaxis or treatment of diabetic complications, which contains a compound of the formula (I), a salt thereof or a prodrug thereof,

23) an agent for prophylaxis or treatment of impaired glucose tolerance, which contains a compound of the formula (I), a salt thereof or a prodrug thereof,

24) an agent for prophylaxis or treatment of obesity, which contains a compound of the formula (I), a salt thereof or a prodrug thereof,

25) a peptidase inhibitor containing a compound of the formula (I), a salt thereof or a prodrug thereof,

26) the inhibitor of 25) above, wherein the peptidase is dipeptidyl peptidase IV,

27) a method of prophylaxis or treatment of diabetes in a mammal, which method comprising administering a compound of the formula (I), a salt thereof or a prodrug thereof to the mammal,

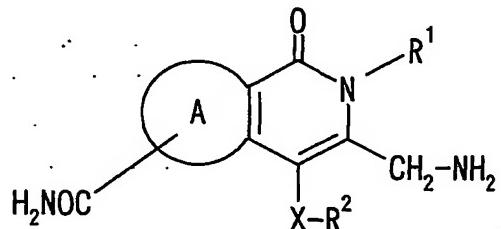
28) a method of prophylaxis or treatment of diabetic complications in a mammal, which method comprising administering a compound of the formula (I), a salt thereof or a prodrug thereof to the mammal,

29) a method of prophylaxis or treatment of impaired glucose tolerance in a mammal, which method comprising administering a compound of the formula (I), a salt thereof or a prodrug thereof to the mammal,

30) a method of prophylaxis or treatment of obesity in a mammal, which method comprising administering a compound of the formula (I), a salt thereof or a prodrug thereof to the mammal,

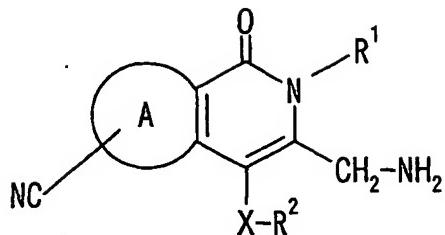
31) a method of inhibiting peptidase in a mammal, which method comprising administering a compound of the

- formula (I), a salt thereof or a prodrug thereof to the mammal,
- 32) use of a compound of the formula (I), a salt thereof or a prodrug thereof for production of an agent for prophylaxis or treatment of diabetes,
- 33) use of a compound of the formula (I), a salt thereof or a prodrug thereof for production of an agent for prophylaxis or treatment of diabetic complications,
- 34) use of a compound of the formula (I), a salt thereof or a prodrug thereof for production of an agent for prophylaxis or treatment of impaired glucose tolerance,
- 35) use of a compound of the formula (I), a salt thereof or a prodrug thereof for production of an agent for prophylaxis or treatment of obesity,
- 36) use of a compound of the formula (I), a salt thereof or a prodrug thereof for production of a peptidase inhibitor;
- 37) a production method of a compound of the formula



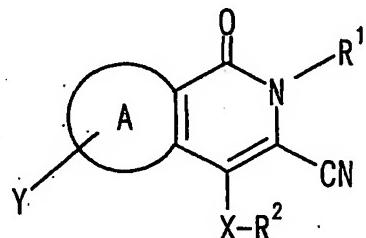
- 20 wherein
- ring A is a 5 to 10-membered aromatic ring;
- R¹ and R² are the same or different and each is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;
- 25 and
- X is a bond, -O-, -S-, -SO-, -SO₂- or -NR³- (R³ is a hydrogen atom or an optionally substituted hydrocarbon group),
- 30 or a salt thereof, which method comprises subjecting a

compound of the formula



wherein the symbols are as defined above, or a salt thereof, to hydrolysis,

5 38) a compound of the formula



wherein

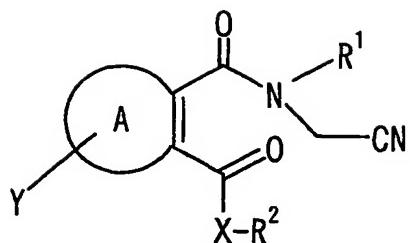
ring A is a 5 to 10-membered aromatic ring;

R¹ and R² are the same or different and each is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;

X is a bond, -O-, -S-, -SO-, -SO₂- or -NR³- (R³ is a hydrogen atom or an optionally substituted hydrocarbon group); and

Y is a halogen atom,
or a salt thereof,

39) a compound of the formula



wherein

ring A is a 5 to 10-membered aromatic ring;

R¹ and R² are the same or different and each is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;

X is a bond, -O-, -S-, -SO-, -SO₂- or -NR³- (R³ is a hydrogen atom or an optionally substituted hydrocarbon group); and

Y is a halogen atom, or a salt thereof, and the like.

DETAILED DESCRIPTION OF THE INVENTION

Each symbol of the formula (I) is described in detail in the following.

The "5 to 10-membered aromatic ring" of the "optionally substituted 5 to 10-membered aromatic ring" for ring A is, for example, a 5 to 10-membered aromatic hydrocarbon ring or a 5 to 10-membered aromatic heterocycle.

Preferable examples of the 5 to 10-membered aromatic hydrocarbon ring include benzene, naphthalene and the like.

Preferable examples of the 5 to 10-membered aromatic heterocycle include a 5 to 10-membered aromatic heterocycle containing 1 to 4 heteroatom(s) selected from an oxygen atom, a sulfur atom and a nitrogen atom as a ring-constituting atom, besides carbon atoms, such as furan, thiophene, pyrrole, oxazole, isoxazole, thiazole, isothiazole, imidazole, pyrazole, 1,2,3-

oxadiazole, furazan, 1,2,3-thiadiazole, 1,2,3-triazole, pyridine, pyridazine, pyrimidine, triazine, benzofuran, isobenzofuran, benzo[b]thiophene, indole, isoindole, 1H-indazole, benzimidazole, benzoxazole, 1,2-benzoisoxazole, 5 benzothiazole, 1,2-benzoisothiazole, 1H-benzotriazole, quinoline, isoquinoline and the like.

The "5 to 10-membered aromatic ring" is preferably a benzene ring, a naphthalene ring, a thiophene ring, a pyridine ring and the like. Of these, a benzene ring is 10 preferable.

The "5 to 10-membered aromatic ring" optionally has 1 to 3 substituent(s) at substitutable position(s). Examples of the substituent include "halogen atom", "nitro group", "cyano group", "C₁₋₃ alkylatedioxy group", 15 "optionally substituted alkyl group having 1 to 10 carbon atom(s)", "optionally substituted alkenyl group having 2 to 10 carbon atoms", "optionally substituted alkynyl group having 2 to 10 carbon atoms", "optionally substituted cycloalkyl group having 3 to 10 carbon atoms", 20 "optionally substituted cycloalkenyl group having 3 to 10 carbon atoms", "optionally substituted cycloalkadienyl group having 4 to 10 carbon atoms", "optionally substituted aryl group having 6 to 14 carbon atoms", "optionally substituted heterocyclic group", 25 "acyl group", "optionally substituted amino group", "optionally substituted hydroxy group", "optionally substituted thiol group", "amidino group" and the like.

As the "halogen atom", for example, fluorine, chlorine, bromine, iodine and the like can be used, with 30 preference given to fluorine, chlorine and bromine.

Examples of the "C₁₋₃ alkylatedioxy group" include methylenedioxy, ethylenedioxy and the like.

As the "alkyl group having 1 to 10 carbon atom(s)" of the "optionally substituted alkyl group having 1 to 35 10 carbon atom(s)", for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, t.-butyl, pentyl,

isopentyl, neopentyl, 1-ethylpropyl, hexyl, isoheptyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl, heptyl, octyl, nonyl, decyl and the like can be used.

- 5 As the "alkenyl group having 2 to 10 carbon atoms" of the "optionally substituted alkenyl group having 2 to 10 carbon atoms", for example, ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 3-hexenyl, 5-hexenyl, 1-heptenyl, 1-octenyl and the like can be used.

- As the "alkynyl group having 2 to 10 carbon atoms" of the "optionally substituted alkynyl group having 2 to 10 carbon atoms", for example, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, 1-heptynyl, 1-octynyl and the like can be used.

- 20 The aforementioned "alkyl group having 1 to 10 carbon atom(s)", "alkenyl group having 2 to 10 carbon atoms" and "alkynyl group having 2 to 10 carbon atoms" optionally have 1 to 3 substituent(s) at substitutable position(s).

- 25 As these substituents, for example, cycloalkyl group having 3 to 10 carbon atoms, aryl group having 6 to 14 carbon atoms (e.g., phenyl, naphthyl and the like), aromatic heterocyclic group (e.g., thienyl, furyl, pyridyl, oxazolyl, thiazolyl, quinolyl and the like), 30 non-aromatic heterocyclic group (e.g., tetrahydrofuryl, morpholino, thiomorpholino, piperidino, pyrrolizinyl, piperazinyl and the like), aralkyl group having 7 to 13 carbon atoms, amino group optionally mono or di-substituted by alkyl having 1 to 4 carbon atom(s) or 35 acyl group having 2 to 8 carbon atoms (e.g., alkanoyl group, alkoxy carbonyl group and the like),

alkylsulfonylamino group having 1 to 8 carbon atom(s), amidino group, acyl group having 2 to 8 carbon atoms (e.g., alkanoyl group, alkoxy carbonyl group and the like), alkylsulfonyl group having 1 to 8 carbon atom(s),
5 carbamoyl group optionally mono or di-substituted by alkyl having 1 to 4 carbon atom(s), sulfamoyl group optionally mono or di-substituted by alkyl having 1 to 4 carbon atom(s), carboxyl group, hydroxy group, alkoxy group having 1 to 6 carbon atom(s) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine and the like), alkenyloxy group having 2 to 5 carbon atoms optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine and the like), cycloalkyloxy group
10 having 3 to 7 carbon atoms, aralkyloxy group having 7 to 13 carbon atoms, aryloxy group having 6 to 14 carbon atoms (e.g., phenoxy, naphthyloxy and the like), thiol group, alkylthio group having 1 to 6 carbon atom(s) optionally substituted by 1 to 3 halogen atom(s) (e.g.,
15 fluorine, chlorine, bromine, iodine and the like), aralkylthio group having 7 to 13 carbon atoms, arylthio group having 6 to 14 carbon atoms (e.g., phenylthio, naphthylthio and the like), sulfo group, cyano group, azide group, nitro group, nitroso group, halogen atom
20 (e.g., fluorine, chlorine, bromine, iodine) and the like can be used.

The "cycloalkyl group having 3 to 10 carbon atoms" of the "optionally substituted cycloalkyl group having 3 to 10 carbon atoms" is, for example, cyclopropyl,
30 cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[3.2.2]nonyl, bicyclo[3.3.1]nonyl, bicyclo[4.2.1]nonyl, bicyclo[4.3.1]decyl and the like.

35 The "cycloalkenyl group having 3 to 10 carbon atoms" of the "optionally substituted cycloalkenyl group

having 3 to 10 carbon atoms" is, for example, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2-cyclohexen-1-yl, 3-cyclohexen-1-yl and the like.

The "optionally substituted cycloalkadienyl group having 4 to 10 carbon atoms" of the "optionally substituted cycloalkadienyl group having 4 to 10 carbon atoms" is, for example, 2,4-cyclopentadien-1-yl, 2,4-cyclohexadien-1-yl, 2,5-cyclohexadien-1-yl and the like.

The "aryl group having 6 to 14 carbon atoms" of the "optionally substituted aryl group having 6 to 14 carbon atoms" is, for example, phenyl, naphthyl, anthryl, phenanthryl, acenaphthylenyl, biphenylyl and the like. Of these, phenyl, 1-naphthyl, 2-naphthyl and the like are preferable.

The "heterocyclic group" of the "optionally substituted heterocyclic group" is exemplified by non-aromatic heterocyclic group and aromatic heterocyclic group.

The non-aromatic heterocyclic group is, for example, 5 to 7-membered monocyclic non-aromatic heterocyclic group or fused non-aromatic heterocyclic group, containing 1 to 4 heteroatom(s) selected from an oxygen atom, a sulfur atom and a nitrogen atom as a ring-constituting atom, besides carbon atoms. The non-aromatic fused heterocycle group is, for example, a group wherein these 5 to 7-membered monocyclic non-aromatic heterocyclic groups and a 6-membered ring containing 1 or 2 nitrogen atom(s), a benzene ring or a 5-membered ring containing one sulfur atom are fused and the like.

Preferable examples of the non-aromatic heterocyclic group include 1-pyrrolizinyl, piperidino, morpholino, thiomorpholino, 1-piperazinyl, hexamethylenimin-1-yl, oxazolidin-3-yl, thiazolidin-3-yl, imidazolidin-3-yl, 2-oxoimidazolidin-1-yl, 2,4-dioxoimidazolidin-3-yl, 2,4-dioxooxazolidin-3-yl, 2,4-

dioxothiazolidin-3-yl, 1,3-dioxoisoindol-2-yl, 5-oxooxadiazol-3-yl, 5-oxothiadiazol-3-yl and the like.

The aromatic heterocyclic group is, for example, a 5 to 7-membered monocyclic aromatic heterocyclic group or fused aromatic heterocyclic group, containing 1 to 4 heteroatom(s) selected from an oxygen atom, a sulfur atom and a nitrogen atom as a ring-constituting atom, besides carbon atoms. The fused aromatic heterocyclic group is, for example, a group where these 5 to 7-membered monocyclic aromatic heterocyclic groups and a 6-membered ring containing 1 or 2 nitrogen atom(s), a benzene ring or a 5-membered ring containing one sulfur atom are fused and the like.

Preferable examples of the aromatic heterocyclic group include 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 2-pyrazinyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, isoxazolyl, isothiazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 1,2,4-oxadiazol-5-yl, 1,3,4-oxadiazol-2-yl, 1,3,4-thiadiazol-2-yl, 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, 1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl, 1,2,3-triazol-4-yl, tetrazol-4-yl, tetrazol-5-yl, 2-quinolyl, 3-quinolyl, 4-quinolyl, 2-quinazolyl, 4-quinazolyl, 2-quinoxalyl, 2-benzofuryl, 3-benzofuryl, 2-benzothienyl, 3-benzothienyl, 2-benzoxazolyl, 2-benzothiazolyl, benzimidazol-1-yl, benzimidazol-2-yl, indol-1-yl, indol-3-yl, 1H-indazol-3-yl, 1H-pyrrolo[2,3-b]pyrazin-2-yl, 1H-pyrrolo[2,3-b]pyridin-6-yl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl, 1H-imidazo[4,5-b]pyrazin-2-yl and the like.

The substituent of the aforementioned "optionally substituted cycloalkyl group having 3 to 10 carbon

atoms", "optionally substituted cycloalkenyl group having 3 to 10 carbon atoms", "optionally substituted cycloalkadienyl group having 4 to 10 carbon atoms", "optionally substituted aryl group having 6 to 14 carbon atoms" and "optionally substituted heterocyclic group" is, for example, alkyl group having 1 to 6 carbon atom(s) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine and the like); alkenyl group having 2 to 6 carbon atoms 10 optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine and the like); cycloalkyl group having 3 to 10 carbon atoms; aryl group having 6 to 14 carbon atoms (e.g., phenyl, naphthyl and the like); aromatic heterocyclic group (e.g., thienyl, 15 furyl, pyridyl, oxazolyl, thiazolyl and the like); non-aromatic heterocyclic group (e.g., tetrahydrofuryl, morpholino, thiomorpholino, piperidino, pyrrolizinyl, piperazinyl and the like); aralkyl group having 7 to 13 carbon atoms; amino group optionally mono or di- 20 substituted by alkyl group having 1 to 4 carbon atom(s) or acyl group having 1 to 15 carbon atom(s) (preferably having 2 to 8 carbon atoms) (e.g., alkanoyl group and the like), such as amino, mono- or di-C₂₋₁₀ alkanoylamino, C₁₋₁₀ alkoxy-carbonylamino, carbamoylamino, mono- or di- 25 C₁₋₁₀ alkyl-carbamoylamino, C₆₋₁₄ aryl-carbonylamino, C₃₋₁₀ cycloalkyl-carbonylamino, C₇₋₁₃ aralkyloxy-carbonylamino, mono- or di-C₁₋₁₀ alkylsulfonylamino, C₆₋₁₄ arylsulfonylamino, C₁₋₆ alkoxy-carbamoylamino and the like; amidino group; acyl group having 2 to 8 carbon 30 atoms (e.g., alkanoyl group and the like); carbamoyl group optionally mono or di-substituted by alkyl group having 1 to 4 carbon atom(s); sulfamoyl group optionally mono or di-substituted by alkyl group having 1 to 4 carbon atom(s); carboxyl group; alkoxycarbonyl group 35 having 2 to 8 carbon atoms; hydroxy group; alkoxy group having 1 to 6 carbon atom(s) optionally substituted by 1

to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine and the like); alkenyloxy group having 2 to 5 carbon atoms optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine and the like); cycloalkyloxy group having 3 to 7 carbon atoms; aralkyloxy group having 7 to 13 carbon atoms; aryloxy group having 6 to 14 carbon atoms (e.g., phenoxy, naphthoxy and the like); thiol group; alkylthio group having 1 to 6 carbon atom(s) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine and the like); aralkylthio group having 7 to 13 carbon atoms; arylthio group having 6 to 14 carbon atoms (e.g., phenylthio, naphthylthio and the like); sulfo group; cyano group; azide group; nitro group; nitroso group; halogen atom (e.g., fluorine, chlorine, bromine, iodine and the like) and the like.

The number of the substituent is, for example, 1 to 3.

The "acyl group" is, for example, a group of the formula: $-COR^4$, $-CO-OR^4$, $-SO_2R^4$, $-SOR^4$, $-PO_3R^4R^5$, $-CO-NR^{4a}R^{5a}$, $-CS-NR^{4a}R^{5a}$ wherein R^4 and R^5 are the same or different and each is hydrogen atom, optionally substituted hydrocarbon group or optionally substituted heterocyclic group. R^{4a} and R^{5a} are the same or different and each is hydrogen atom, optionally substituted hydrocarbon group or optionally substituted heterocyclic group and R^{4a} and R^{5a} may form, together with the adjacent nitrogen atom, an optionally substituted, nitrogen-containing heterocycle, and the like.

The "optionally substituted hydrocarbon group" for R^4 , R^5 , R^{4a} and R^{5a} is exemplified by "optionally substituted alkyl group having 1 to 10 carbon atom(s)", "optionally substituted alkenyl group having 2 to 10 carbon atoms", "optionally substituted alkynyl group having 2 to 10 carbon atoms", "optionally substituted cycloalkyl group having 3 to 10 carbon atoms", "optionally substituted cycloalkenyl group having 3 to

10 carbon atoms", "optionally substituted cycloalkadienyl group having 4 to 10 carbon atoms", "optionally substituted aryl group having 6 to 14 carbon atoms", "optionally substituted aralkyl group having 7 to 13 carbon atoms", "optionally substituted arylalkenyl group having 8 to 13 carbon atoms" and the like, which are mentioned as the substituents in ring A.

The "aralkyl group having 7 to 13 carbon atoms" of the "optionally substituted aralkyl group having 7 to 13 carbon atoms" is, for example, benzyl, phenethyl, naphthylmethyl and the like.

The "arylalkenyl group having 8 to 13 carbon atoms" of the "optionally substituted arylalkenyl group having 8 to 13 carbon atoms" is, for example, styryl and the like.

The substituent of the "optionally substituted aralkyl group having 7 to 13 carbon atoms" and "optionally substituted arylalkenyl group having 8 to 13 carbon atoms" is exemplified by that mentioned as the substituent in the aforementioned "optionally substituted cycloalkyl group having 3 to 10 carbon atoms" and the like. The number of the substituent is, for example, 1 to 3.

The "optionally substituted heterocyclic group" for R⁴, R⁵, R^{4a} or R^{5a} is exemplified by that mentioned as the substituent in ring A.

The "nitrogen-containing heterocycle" of the "optionally substituted, nitrogen-containing heterocycle" formed by R^{4a} and R^{5a} together with the adjacent nitrogen atom is, for example, a 5 to 7-membered, nitrogen-containing heterocycle containing at least one nitrogen atom and further 1 or 2 heteroatom(s) selected from oxygen atom, sulfur atom and nitrogen atom as a ring-constituting atom, besides carbon atoms.

Preferable examples of the nitrogen-containing heterocycle include pyrrolidine, imidazolidine,

pyrazolidine, piperidine, piperazine, morpholine, thiomorpholine and the like.

The nitrogen-containing heterocycle optionally has 1 or 2 substituent(s) at substitutable position(s).

- 5 Examples of the substituent include hydroxy group, C₁₋₆ alkyl group optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine and the like), C₇₋₁₃ aralkyl group (e.g., benzyl, diphenylmethyl and the like) and the like.
- 10 Preferable examples of the "acyl group" include formyl, carboxyl, carbamoyl, C₁₋₆ alkyl-carbonyl (e.g., acetyl, isobutanoyl, isopentanoyl and the like), C₁₋₆ alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl and the like), C₆₋₁₄ aryl-carbonyl (e.g., benzoyl, 1-naphthoyl, 2-naphthoyl and the like), C₆₋₁₄ aryloxy-carbonyl (e.g., phenoxy carbonyl, naphthoxy carbonyl and the like), C₇₋₁₃ aralkyloxy-carbonyl (e.g., benzyloxycarbonyl, phenethyloxycarbonyl and the like), mono- or di- (C₁₋₆ alkyl optionally having 1 to 3 substituent(s) selected from halogen atom and C₁₋₆ alkoxy-carbonyl)-carbamoyl (e.g., methylcarbamoyl, ethylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl, propylcarbamoyl, trifluoroethylcarbamoyl and the like), C₆₋₁₄ aryl-carbamoyl (e.g., phenylcarbamoyl and the like), C₃₋₁₀ cycloalkyl-carbamoyl (e.g., cyclopropylcarbamoyl and the like), C₇₋₁₃ aralkyl-carbamoyl (e.g., benzylcarbamoyl and the like), C₁₋₆ alkylsulfonyl (e.g., methylsulfonyl and the like), C₆₋₁₄ arylsulfonyl (e.g., phenylsulfonyl and the like), nitrogen-containing heterocycle-carbonyl optionally substituted by hydroxy (e.g., pyrrolidinylcarbonyl, piperidinocarbonyl and the like), C₁₋₆ alkylsulfinyl (e.g., methylsulfinyl and the like),
- 35 C₁₋₆ alkoxy-carbamoyl (e.g., methoxycarbamoyl), aminocarbamoyl, hydroxycarbamoyl, thiocarbamoyl and the

like.

The "optionally substituted amino group" is, for example, amino group optionally substituted by 1 or 2 substituent(s) selected from alkyl group having 1 to 10 carbon atom(s), alkenyl group having 2 to 10 carbon atoms, cycloalkyl group having 3 to 10 carbon atoms, cycloalkenyl group having 3 to 10 carbon atoms, aryl group having 6 to 14 carbon atoms and acyl.

The "alkyl group having 1 to 10 carbon atom(s)", "alkenyl group having 2 to 10 carbon atoms", "cycloalkyl group having 3 to 10 carbon atoms", "cycloalkenyl group having 3 to 10 carbon atoms", "aryl group having 6 to 14 carbon atoms" and "acyl group" are exemplified by those mentioned as the substituent in ring A.

Preferable examples of the substituted amino group include mono- or di-C₁₋₁₀ alkylamino (e.g., methylamino, dimethylamino, ethylamino, diethylamino, propylamino, dibutylamino), mono- or di-C₂₋₁₀ alkenylamino (e.g., diallylamino), mono- or di-C₃₋₁₀ cycloalkylamino (e.g., cyclohexylamino), mono- or di-C₂₋₁₀ alkanoylamino (e.g., acetylamino, propionylamino, butanoylamino, isobutanoylamino, isopentanoylamino), C₆₋₁₄ arylcarbonylamino (e.g., benzoylamino), C₆₋₁₄ arylamino (e.g., phenylamino), carbamoylamino, mono- or di-C₁₋₁₀ alkylcarbamoylamino (e.g., methylcarbamoylamino, dimethylcarbamoylamino), C₁₋₁₀ alkoxy-carbonylamino (e.g., methoxycarbonylamino), C₇₋₁₃ aralkyloxy-carbonylamino (e.g., benzyloxycarbonylamino), C₃₋₁₀ cycloalkylcarbonylamino (e.g., cyclopentylcarbonylamino, cyclohexylcarbonylamino), mono- or di-C₁₋₁₀ alkylsulfonylamino (e.g., methylsulfonylamino, dimethylsulfonylamino), C₆₋₁₄ arylsulfonylamino (e.g., phenylsulfonylamino), C₁₋₆ alkoxy-carbamoylamino (e.g., methoxycarbamoylamino) and the like.

The "optionally substituted hydroxy group" is, for example, hydroxy group optionally substituted by "alkyl"

group having 1 to 10 carbon atom(s)", "alkenyl group having 2 to 10 carbon atoms", "alkynyl group having 2 to 10 carbon atoms", "cycloalkyl group having 3 to 10 carbon atoms", "cycloalkenyl group having 3 to 10 carbon atoms", "aryl group having 6 to 14 carbon atoms" or 5 "aralkyl group having 7 to 13 carbon atoms", each of which is optionally substituted.

The "alkyl having 1 to 10 carbon atom(s)", "alkenyl group having 2 to 10 carbon atoms", "alkynyl group 10 having 2 to 10 carbon atoms", "cycloalkyl group having 3 to 10 carbon atoms", "cycloalkenyl group having 3 to 10 carbon atoms", "aryl group having 6 to 14 carbon atoms" and "aralkyl having 7 to 13 carbon atoms" are exemplified by those mentioned as the aforementioned R⁴ 15 and the like.

These "alkyl group having 1 to 10 carbon atom(s)", "alkenyl group having 2 to 10 carbon atoms", "alkynyl group having 2 to 10 carbon atoms", "cycloalkyl group having 3 to 10 carbon atoms", "cycloalkenyl group having 20 3 to 10 carbon atoms", "aryl group having 6 to 14 carbon atoms" and "aralkyl group having 7 to 13 carbon atoms" each optionally have 1 to 3 substituent(s) at substitutable position(s). Such substituents are, for example, halogen atom (e.g., fluorine, chlorine, bromine, 25 iodine and the like), alkoxy group having 1 to 3 carbon atom(s), alkoxycarbonyl group having 2 to 5 carbon atoms, alkanoyl group having 2 to 5 carbon atoms, cyano group, carbamoyl group, hydroxy group, cycloalkyl group having 3 to 10 carbon atoms, carboxyl group, amino group, 30 alkanoylamino group having 2 to 5 carbon atoms and the like.

The substituted hydroxy group is preferably "alkoxy group having 1 to 10 carbon atom(s)", "alkenyloxy group having 2 to 10 carbon atoms", "alkynyloxy group having 2 35 to 10 carbon atoms", "cycloalkyloxy group having 3 to 10 carbon atoms", "cycloalkenyloxy group having 3 to 10

carbon atoms", "aryloxy group having 6 to 14 carbon atoms", "aralkyloxy group having 7 to 13 carbon atoms" and the like, each optionally having 1 to 3 substituent(s) selected from halogen atom (e.g., 5 fluorine, chlorine, bromine, iodine and the like), alkoxy group having 1 to 3 carbon atom(s), alkoxycarbonyl group having 2 to 5 carbon atoms, alkanoyl group having 2 to 5 carbon atoms, cyano group, carbamoyl group, hydroxy group, carboxyl group, amino 10 group, alkanoylamino group having 2 to 5 carbon atoms and cycloalkyl group having 3 to 10 carbon atoms.

The "alkoxy group having 1 to 10 carbon atom(s)" is, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec.-butoxy, t.-butoxy, pentyloxy, 15 isopentyloxy, neopentyloxy, hexyloxy, heptyloxy, nonyloxy and the like.

The "alkenyloxy group having 2 to 10 carbon atoms" is, for example, allyloxy, crotyloxy, 2-pentenyloxy, 3-hexenyloxy and the like.

20 The "alkynyloxy group having 2 to 10 carbon atoms" is, for example, ethynyoxy, propinyloxy, pentinyloxy and the like.

The "cycloalkyloxy group having 3 to 10 carbon atoms" is, for example, cyclobutoxy, cyclopentyloxy, 25 cyclohexyloxy and the like.

The "cycloalkenyloxy group having 3 to 10 carbon atoms" is, for example, 2-cyclopentenyloxy, 2-cyclohexenyloxy and the like.

The "aryloxy group having 6 to 14 carbon atoms" is, 30 for example, phenoxy, naphthyloxy and the like.

The "aralkyloxy group having 7 to 13 carbon atoms" is, for example, benzyloxy, phenethyloxy, naphthylmethyloxy and the like.

The substituted hydroxy group is more preferably 35 "alkoxy group having 1 to 10 carbon atom(s)", "cycloalkyloxy group having 3 to 10 carbon atoms" or

- "aralkyloxy group having 7 to 13 carbon atoms", each optionally having 1 to 3 substituent(s) selected from halogen atom (e.g., fluorine, chlorine, bromine, iodine and the like), alkoxy group having 1 to 3 carbon atom(s),
- 5 alkoxycarbonyl group having 2 to 5 carbon atoms, alkanoyl group having 2 to 5 carbon atoms, cyano group, carbamoyl group, hydroxy group, carboxyl group, amino group, alkanoylamino group having 2 to 5 carbon atoms and cycloalkyl group having 3 to 10 carbon atoms.

10 The "optionally substituted thiol group" is, for example, thiol group optionally substituted by "alkyl group having 1 to 10 carbon atom(s)", "alkenyl group having 2 to 10 carbon atoms", "alkynyl group having 2 to 10 carbon atoms", "cycloalkyl group having 3 to 10 carbon atoms", "cycloalkenyl group having 3 to 10 carbon atoms", "aryl group having 6 to 14 carbon atoms" or "aralkyl group having 7 to 13 carbon atoms", each of which is optionally substituted.

These "alkyl group having 1 to 10 carbon atom(s)",
20 "alkenyl group having 2 to 10 carbon atoms", "alkynyl group having 2 to 10 carbon atoms", "cycloalkyl group having 3 to 10 carbon atoms", "cycloalkenyl group having 3 to 10 carbon atoms", "aryl group having 6 to 14 carbon atoms" and "aralkyl group having 7 to 13 carbon atoms"
25 are exemplified by those mentioned as the aforementioned R⁴ and the like.

These "alkyl group having 1 to 10 carbon atom(s)", "alkenyl group having 2 to 10 carbon atoms", "alkynyl group having 2 to 10 carbon atoms", "cycloalkyl group having 3 to 10 carbon atoms", "cycloalkenyl group having 3 to 10 carbon atoms", "aryl group having 6 to 14 carbon atoms" and "aralkyl group having 7 to 13 carbon atoms" each optionally have 1 to 3 substituent(s) at substitutable position(s). These substituents are, for
35 example, halogen atom (e.g., fluorine, chlorine, bromine, iodine and the like), alkoxy group having 1 to 3 carbon

atom(s), alkoxycarbonyl group having 2 to 5 carbon atoms, alkanoyl group having 2 to 5 carbon atoms, cyano group, carbamoyl group, hydroxy group, cycloalkyl group having 3 to 10 carbon atoms, carboxyl group, amino group,
5 alkanoylamino group having 2 to 5 carbon atoms and the like.

The substituted thiol group is preferably "alkylthio group having 1 to 10 carbon atom(s)", "alkenylthio group having 2 to 10 carbon atoms",
10 "alkynylthio group having 2 to 10 carbon atoms", "cycloalkylthio group having 3 to 10 carbon atoms", "cycloalkenylthio group having 3 to 10 carbon atoms", "arylthio group having 6 to 14 carbon atoms ", "aralkylthio group having 7 to 13 carbon atoms" and the like, each optionally having 1 to 3 substituent(s) selected from halogen atom (e.g., fluorine, chlorine, bromine, iodine and the like), alkoxy group having 1 to 3 carbon atom(s), alkoxycarbonyl group having 2 to 5 carbon atoms, alkanoyl group having 2 to 5 carbon atoms,
15 cyano group, carbamoyl group, hydroxy group, carboxyl group, amino group, alkanoylamino group having 2 to 5 carbon atoms and cycloalkyl group having 3 to 10 carbon atoms.

The "alkylthio group having 1 to 10 carbon atom(s)" is, for example, methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec.-butylthio, t.-butylthio, pentylthio, isopentylthio, neopentylthio, hexylthio, heptylthio, nonylthio and the like.

The "alkenylthio group having 2 to 10 carbon atoms" is, for example, allylthio, crotylthio, 2-pentenylthio, 3-hexenylthio and the like.

The "alkynylthio group having 2 to 10 carbon atoms" is, for example, ethynylthio, propinylthio, pentinylthio and the like.

35 The "cycloalkylthio group having 3 to 10 carbon atoms" is, for example, cyclobutylthio, cyclopentylthio,

cyclohexylthio and the like.

The "cycloalkenylthio group having 3 to 10 carbon atoms" is, for example, 2-cyclopentenylthio, 2-cyclohexenylthio and the like.

5 The "arylthio group having 6 to 14 carbon atoms" is, for example, phenylthio, naphthylthio and the like.

The "aralkylthio having 7 to 13 carbon atoms" is, for example, benzylthio, phenethylthio, naphthylmethylthio and the like.

10 The substituted thiol group is more preferably alkylthio group having 1 to 10 carbon atom(s) optionally substituted by carbamoyl group.

Preferable examples of the "substituent" of "5 to 10-membered aromatic ring" for ring A are

15 1) a halogen atom (e.g., fluorine, chlorine, bromine, iodine and the like);

2) a nitro group;

3) a cyano group;

4) a C₁₋₃ alkylenedioxy group (e.g., methylenedioxy);

20 5) a C₁₋₁₀ alkyl group (e.g., methyl, ethyl) or a C₂₋₁₀ alkenyl group (e.g., ethenyl), each optionally having 1 to 3 substituent(s) selected from halogen atom, hydroxy group, carboxyl group, alkoxy carbonyl group having 2 to 8 carbon atoms (e.g., ethoxycarbonyl), carbamoyl group,

25 cyano group, amino group, alkanoylamino group having 2 to 8 carbon atoms (e.g., acetyl amino, isobutanoylamino), alkoxy carbonylamino group having 2 to 8 carbon atoms (e.g., ethoxycarbonylamino) and alkylsulfonylamino group having 1 to 8 carbon atom(s) (e.g.,

30 methylsulfonylamino);

6) an optionally substituted hydroxy group [e.g., alkoxy group having 1 to 10 carbon atom(s) (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy), cycloalkyloxy group having 3 to 10 carbon atoms (e.g.,

35 cyclopentyloxy) or aralkyloxy group having 7 to 13 carbon atoms (e.g., benzyloxy), each optionally having 1

to 3 substituent(s) selected from halogen atom, alkoxy group having 1 to 3 carbon atom(s) (e.g., methoxy), alkoxycarbonyl group having 2 to 5 carbon atoms (e.g., methoxycarbonyl, ethoxycarbonyl), alkanoyl group having 5 to 10 carbon atoms (e.g., pivaloyl), cyano group, carbamoyl group, hydroxy group, carboxyl group, amino group, alkanoylamino group having 2 to 5 carbon atoms (e.g., acetylarnino) and cycloalkyl group having 3 to 10 carbon atoms (e.g., cyclopropyl, cyclohexyl); hydroxy group];

7) an acyl group [e.g., formyl, carboxyl, C₁₋₆ alkylcarbonyl (e.g., acetyl), C₁₋₆ alkoxy-carbonyl (e.g., methoxycarbonyl), carbamoyl, aminocarbamoyl, hydroxycarbamoyl, mono- or di-(C₁₋₆ alkyl optionally having 1 to 3 substituent(s) selected from halogen atom and C₁₋₆ alkoxy-carbonyl (e.g., ethoxycarbonyl))-carbamoyl (e.g., methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, dimethylcarbamoyl, trifluoroethylcarbamoyl, ethoxycarbonylmethylcarbamoyl and the like), C₃₋₁₀ cycloalkyl-carbamoyl (e.g., cyclopropylcarbamoyl), C₇₋₁₃ aralkyl-carbamoyl (e.g., benzylcarbamoyl), nitrogen-containing heterocycle-carbonyl optionally substituted by hydroxy (e.g., pyrrolidinylcarbonyl, piperidinocarbonyl), C₁₋₆ alkylsulfonyl (e.g., methylsulfonyl), C₁₋₆ alkylsulfinyl (e.g., methylsulfinyl), thiocarbamoyl];

8) an optionally substituted amino group [e.g., amino, mono- or di-C₂₋₁₆ alkanoylamino (e.g., acetylarnino, propionylarnino, isobutanoylamino, isopentanoylamino), C₁₋₁₀ alkoxy-carbonylamino (e.g., methoxycarbonylamino), carbamoylamino, mono- or di-C₁₋₁₀ alkyl-carbamoylamino (e.g., methylcarbamoylamino, dimethylcarbamoylamino), C₆₋₁₄ aryl-carbonylamino (e.g., benzoylamino), C₃₋₁₀ cycloalkyl-carbonylamino (e.g., cyclopentylcarbonylamino), C₇₋₁₃ aralkyloxy-carbonylamino (e.g., benzyloxycarbonylamino), mono- or di-C₁₋₁₀

- alkylsulfonylamino (e.g., methylsulfonylamino, dimethylsulfonylamino), C₆₋₁₄ arylsulfonylamino (e.g., phenylsulfonylamino), C₁₋₆ alkoxy-carbamoylamino (e.g., methoxycarbamoylamino)];
- 5 9) an aryl group having 6 to 14 carbon atoms (e.g., phenyl);
- 10) an optionally substituted thiol group [e.g., alkylthio group having 1 to 10 carbon atom(s) optionally substituted by carbamoyl group (e.g., methylthio)];
- 10 11) an optionally substituted heterocyclic group [e.g., aromatic heterocyclic group (preferably furyl, thieryl, oxazolyl, oxadiazolyl, thiazolyl, tetrazolyl, pyridyl, pyrrolyl, triazolyl) or non-aromatic heterocyclic group (preferably dioxoisoindole, 5-oxoadiazol-3-yl, 5-oxothiadiazol-3-yl), each optionally having 1 or 2 substituent(s) selected from C₁₋₆ alkyl group optionally substituted by 1 to 3 halogen atom(s) (e.g., methyl, trifluoromethyl), carboxyl group, alkoxy carbonyl group having 2 to 8 carbon atoms (preferably ethoxycarbonyl),
- 15 cyano group, carbamoyl group, amino group, mono- or di-C₂₋₁₀ alkanoylamino group (e.g., acetylamino, isopentanoylamino), C₁₋₁₀ alkoxy-carbonylamino group (e.g., methoxycarbonylamino), carbamoylamino group, mono- or di-C₁₋₁₀ alkyl-carbamoylamino group (e.g.,
- 20 methylcarbamoylamino, dimethylcarbamoylamino), C₆₋₁₄ aryl-carbonylamino group (e.g., benzoylamino), C₃₋₁₀ cycloalkyl-carbonylamino group, C₇₋₁₃ aralkyloxy-carbonylamino group, mono- or di-C₁₋₁₀ alkylsulfonylamino group (e.g., methylsulfonylamino, dimethylsulfonylamino),
- 25 C₆₋₁₄ arylsulfonylamino group and C₁₋₆ alkoxy-carbamoylamino group (e.g., methoxycarbamoylamino)];
- 30 12) an amidino group;
- and the like.

The number of substituent is preferably 1 to 3,
35 more preferably 1 or 2.

The "substituent" of the "5 to 10-membered aromatic

- ring" for ring A is preferably
- 1) a halogen atom (e.g., fluorine, chlorine, bromine, iodine and the like);
 - 2) a nitro group;
 - 3) a cyano group;
 - 4) a C₁₋₃ alkylenedioxy group (e.g., methylenedioxy);
 - 5) a C₁₋₁₀ alkyl group or a C₂₋₁₀ alkenyl group, each optionally having 1 to 3 substituent(s) selected from halogen atom, hydroxy group, carboxyl group,
 - 10 alkoxycarbonyl group having 2 to 8 carbon atoms, carbamoyl group, cyano group, amino group, alkanoylamino group having 2 to 8 carbon atoms, alkoxycarbonylamino group having 2 to 8 carbon atoms, alkylsulfonylamino group having 1 to 8 carbon atoms;
 - 15 6) an optionally substituted hydroxy group (e.g., alkoxy group having 1 to 10 carbon atom(s), cycloalkyloxy group having 3 to 10 carbon atoms or aralkyloxy group having 7 to 13 carbon atoms, each optionally having 1 to 3 substituent(s) selected from halogen atom, alkoxy group
 - 20 having 1 to 3 carbon atom(s), alkoxycarbonyl group having 2 to 5 carbon atoms, alkanoyl group having 2 to 5 carbon atoms, cyano group, carbamoyl group, hydroxy group, carboxyl group and cycloalkyl group having 3 to 10 carbon atoms; hydroxy group);
 - 25 7) an acyl group (e.g., carboxyl, C₁₋₆ alkoxy-carbonyl, carbamoyl, mono- or di-(C₁₋₆ alkyl optionally having 1 to 3 substituent(s) selected from halogen atom and C₁₋₆ alkoxy-carbonyl)-carbamoyl, C₃₋₁₀ cycloalkyl-carbamoyl, C₇₋₁₃ aralkyl-carbamoyl, nitrogen-containing heterocycle-
 - 30 carbonyl optionally substituted by hydroxy, C₁₋₆ alkyl-carbonyl, thiocarbamoyl, C₁₋₆ alkylsulfonyl, C₁₋₆ alkylsulfinyl);
 - 35 8) an optionally substituted amino group (e.g., amino, mono- or di-C₂₋₁₀ alkanoylamino, C₁₋₁₀ alkoxy-carbonylamino, mono- or di-C₁₋₁₀ alkyl-carbamoylamino, C₆₋₁₄ aryl-carbonylamino, C₃₋₁₀ cycloalkyl-carbonylamino, C₇₋₁₃

- aralkyloxy-carbonylamino, mono- or di-C₁₋₁₀ alkylsulfonylamino, C₆₋₁₄ arylsulfonylamino, carbamoylamino); or
- 9) an optionally substituted heterocyclic group [e.g.,
- 5] aromatic heterocyclic group (preferably furyl, thienyl, oxazolyl, oxadiazolyl, thiazolyl, tetrazolyl, pyridyl, pyrrolyl, triazolyl) or non-aromatic heterocyclic group (preferably dioxoisoindole, 5-oxooxadiazol-3-yl, 5-oxothiadiazol-3-yl)], each optionally having 1 or 2
- 10 substituent(s) selected from C₁₋₆ alkyl group optionally substituted by 1 to 3 halogen atom(s), carboxyl group, alkoxy carbonyl group having 2 to 8 carbon atoms, cyano group, carbamoyl group, amino group, mono- or di-C₂₋₁₀ alkanoylamino group, C₁₋₁₀ alkoxy-carbonylamino group,
- 15 carbamoylamino group, mono- or di-C₁₋₁₀ alkyl-carbamoylamino group, C₆₋₁₄ aryl-carbonylamino group, C₃₋₁₀ cycloalkyl-carbonylamino group, C₇₋₁₃ aralkyloxy-carbonylamino group, mono- or di-C₁₋₁₀ alkylsulfonylamino group, C₆₋₁₄ arylsulfonylamino group and C₁₋₆ alkoxy-
- 20 carbamoylamino group.

The number of substituent is preferably 1 to 3, more preferably 1 or 2.

The "substituent" of the "5 to 10-membered aromatic ring" for ring A is more preferably

- 25 1) a halogen atom (e.g., fluorine, chlorine, bromine, iodine and the like);
- 2) a nitro group;
- 3) a cyano group;
- 4) a C₁₋₃ alkylenedioxy group (e.g., methylenedioxy);
- 30 5) an optionally substituted hydroxy group (preferably methoxy, carbamoylmethoxy and the like);
- 6) an acyl group (preferably carbamoyl, methoxycarbonyl and the like);
- 7) an optionally substituted amino group (preferably
- 35 acetyl amino and the like);
- 8) a C₁₋₁₀ alkyl group (preferably ethyl) or a C₂₋₁₀

alkenyl group (preferably ethenyl), each optionally substituted by carbamoyl group;

9) an optionally substituted heterocyclic group [e.g., aromatic heterocyclic group (preferably furyl, thieryl,

5 oxazolyl, oxadiazolyl, thiazolyl, tetrazolyl, pyridyl, pyrrolyl, triazolyl) or non-aromatic heterocyclic group (preferably dioxoisoindole, 5-oxooxadiazol-3-yl, 5-oxothiadiazol-3-yl), each optionally having 1 or 2 substituent(s) selected from C₁₋₆ alkyl group optionally

10 substituted by 1 to 3 halogen atom(s), carboxyl group, alkoxycarbonyl group having 2 to 8 carbon atoms, cyano group, carbamoyl group, amino group, mono- or di-C₂₋₁₀ alkanoylamino group, C₁₋₁₀ alkoxy-carbonylamino group, carbamoylamino group, mono- or di-C₁₋₁₀ alkyl-

15 carbamoylamino group, C₆₋₁₄ aryl-carbonylamino group, C₃₋₁₀ cycloalkyl-carbonylamino group, C₇₋₁₃ aralkyloxy-carbonylamino group, mono- or di-C₁₋₁₀ alkylsulfonylamino group, C₆₋₁₄ arylsulfonylamino group and C₁₋₆ alkoxy-carbamoylamino group]. The number of substituent is

20 preferably 1 or 2.

The ring A is preferably benzene ring optionally having 1 or 2 substituent(s) selected from:

1) a cyano group;

2) a C₁₋₁₀ alkyl group (preferably ethyl) or a C₂₋₁₀ alkenyl group (preferably ethenyl), each optionally having 1 to 3 substituent(s) selected from carbamoyl group, carboxyl group and alkoxycarbonyl group having 2 to 8 carbon atoms (preferably methoxycarbonyl);

25 3) an optionally substituted hydroxy group [preferably alkoxy group having 1 to 10 carbon atom(s) (preferably methoxy, isopropoxy) optionally having 1 to 3 substituent(s) selected from carbamoyl group, carboxyl group and alkoxycarbonyl group having 2 to 5 carbon atoms (preferably methoxycarbonyl); hydroxy group;

30 35 aralkyloxy group having 7 to 13 carbon atoms (preferably benzyloxy)] [more preferably carbamoylmethoxy];

- 4) an acyl group [preferably C₁₋₆ alkyl-carbonyl (preferably acetyl), carbamoyl, mono- or di- (C₁₋₆ alkyl optionally having 1 to 3 substituent(s) selected from halogen atom and C₁₋₆ alkoxy-carbonyl)-carbamoyl]
- 5 (preferably methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, dimethylcarbamoyl, trifluoroethylcarbamoyl, ethoxycarbonylmethylcarbamoyl and the like), C₃₋₁₀ cycloalkyl-carbamoyl (preferably cyclopropylcarbamoyl), C₇₋₁₃ aralkyl-carbamoyl
- 10 (preferably benzylcarbamoyl), nitrogen-containing heterocycle-carbonyl optionally substituted by hydroxy (preferably pyrrolidinylcarbonyl, piperidinocarbonyl), C₁₋₆ alkylsulfonyl (preferably methylsulfonyl), C₁₋₆ alkylsulfinyl (preferably methylsulfinyl), carboxyl, C₁₋₆
- 15 alkoxy-carbonyl (preferably methoxycarbonyl), thiocarbamoyl];
- 5) an optionally substituted amino group (preferably carbamoylamino);
- 6) an optionally substituted thiol group [preferably
- 20 alkylthio group having 1 to 10 carbon atom(s) optionally substituted by carbamoyl group (preferably methylthio)];
- 7) an optionally substituted heterocyclic group [preferably aromatic heterocyclic group (preferably furyl, thienyl, oxazolyl, oxadiazolyl, thiazolyl,
- 25 tetrazolyl, pyridyl, pyrrolyl, triazolyl) or non-aromatic heterocyclic group (preferably dioxoisindole, 5-oxooxadiazol-3-yl, 5-oxothiadiazol-3-yl), each optionally having 1 or 2 substituent(s) selected from C₁₋₆ alkyl group optionally substituted by 1 to 3 halogen
- 30 atom(s) (preferably methyl, trifluoromethyl), carboxyl group, alkoxy carbonyl group having 2 to 8 carbon atoms (preferably ethoxycarbonyl), cyano group, carbamoyl group, amino group, mono- or di-C₂₋₁₀ alkanoylamino group (e.g., acetylarnino, isopentanoylamino), C₁₋₁₀ alkoxy-
- 35 carbonylamino group (e.g., methoxycarbonylamino), carbamoylamino group, mono- or di-C₁₋₁₀ alkyl-

- carbamoylamino group (e.g., methylcarbamoylamino, dimethylcarbamoylamino), C₆₋₁₄ aryl-carbonylamino group (e.g., benzoylamino), C₃₋₁₀ cycloalkyl-carbonylamino group, C₇₋₁₃ aralkyloxy-carbonylamino group, mono- or di-
5 C₁₋₁₀ alkylsulfonylamino group (e.g., methylsulfonylamino, dimethylsulfonylamino), C₆₋₁₄ arylsulfonylamino group and C₁₋₆ alkoxy-carbamoylamino group (e.g., methoxycarbamoylamino)]; and
8) an amidino group.
- 10 The ring A is more preferably a benzene ring having 1 or 2 substituent(s) selected from
1) a C₁₋₁₀ alkyl group (preferably ethyl) or a C₂₋₁₀ alkenyl group (preferably ethenyl), each having 1 to 3 substituent(s) selected from carbamoyl group, carboxyl
15 group and alkoxy carbonyl group having 2 to 8 carbon atoms (preferably methoxycarbonyl);
2) an optionally substituted hydroxy group [preferably alkoxy group having 1 to 10 carbon atom(s) (preferably methoxy, isopropoxy) optionally having 1 to 3
20 substituent(s) selected from carbamoyl group, carboxyl group and alkoxy carbonyl group having 2 to 5 carbon atoms (preferably methoxycarbonyl); hydroxy group; aralkyloxy group having 7 to 13 carbon atom(s) (preferably benzyloxy)] [more preferably
25 carbamoylmethoxy];
3) an acyl group [preferably C₁₋₆ alkyl-carbonyl (preferably acetyl), carbamoyl, mono- or di- (C₁₋₆ alkyl optionally having 1 to 3 substituent(s) selected from halogen atom and C₁₋₆ alkoxy-carbonyl)-carbamoyl]
30 (preferably methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, dimethylcarbamoyl, trifluoroethylcarbamoyl, ethoxycarbonylmethylcarbamoyl and the like), C₃₋₁₀ cycloalkyl-carbamoyl (preferably cyclopropylcarbamoyl), C₇₋₁₃ aralkyl-carbamoyl
35 (preferably benzylcarbamoyl), nitrogen-containing heterocycle-carbonyl optionally substituted by hydroxy

(preferably pyrrolidinylcarbonyl, piperidinocarbonyl), C₁₋₆ alkylsulfonyl (preferably methylsulfonyl), C₁₋₆ alkylsulfinyl (preferably methylsulfinyl), carboxyl, C₁₋₆ alkoxy-carbonyl (preferably methoxycarbonyl), 5 thiocabamoyl]; and
4) an optionally substituted heterocyclic group [preferably aromatic heterocyclic group (preferably furyl, thienyl, oxazolyl, oxadiazolyl, thiazolyl, tetrazolyl, pyridyl, pyrrolyl, triazolyl) or non-aromatic heterocyclic group (preferably dioxoisooindole, 5-oxooxadiazol-3-yl, 5-oxothiadiazol-3-yl), each optionally having 1 or 2 substituent(s) selected from C₁₋₆ alkyl optionally substituted by 1 to 3 halogen atom(s) (preferably methyl, trifluoromethyl), carboxyl group, 15 alkoxycarbonyl group having 2 to 8 carbon atoms (preferably ethoxycarbonyl), cyano group, carbamoyl group, amino, mono- or di-C₂₋₁₀ alkanoylamino (e.g., acetylamino, isopentanoylamino), C₁₋₁₀ alkoxy-carbonylamino (e.g., methoxycarbonylamino), 20 carbamoylamino, mono- or di-C₁₋₁₀ alkyl-carbamoylamino (e.g., methylcarbamoylamino, dimethylcarbamoylamino), C₆₋₁₄ aryl-carbonylamino (e.g., benzoylamino), C₃₋₁₀ cycloalkyl-carbonylamino, C₇₋₁₃ aralkyloxy-carbonylamino, mono- or di-C₁₋₁₀ alkylsulfonylamino (e.g., 25 methylsulfonylamino, dimethylsulfonylamino), C₆₋₁₄ arylsulfonylamino and C₁₋₆ alkoxy-carbamoylamino (e.g., methoxycarbamoylamino)].

Examples of the "optionally substituted hydrocarbon group" for R¹ and R² are those exemplified for the 30 aforementioned R⁴ and the like.

Examples of the "optionally substituted heterocyclic group" for R¹ and R² are those exemplified as the substituent in ring A.

R¹ is preferably an optionally substituted 35 hydrocarbon and more preferably an alkyl group having 1 to 10 carbon atom(s) which is optionally substituted by

cycloalkyl group having 3 to 10 carbon atoms (e.g., cyclopropyl and the like). R¹ is particularly preferably an alkyl group having 4 to 10 carbon atoms or a cycloalkylalkyl group having 4 to 10 carbon atoms

- 5 (preferably cyclopropylmethyl). Of these, preferred is an alkyl group having 4 or 5 carbon atoms (e.g., butyl, isobutyl, sec.-butyl, t.-butyl, pentyl, isopentyl, neopentyl, 1-ethylpropyl and the like).

R² is preferably an optionally substituted

- 10 hydrocarbon group. More preferably, R² is an alkyl group having 1 to 10 substituent(s) (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, t.-butyl, pentyl and the like), aryl group having 6 to 14 carbon atoms (e.g., phenyl and the like) or aralkyl group
15 having 7 to 13 carbon atoms (e.g., benzyl, phenethyl, naphthylmethyl and the like), each optionally having 1 to 3 (preferably 1 or 2) substituent(s) selected from halogen atom (e.g., fluorine, chlorine and the like), hydroxy group, nitro group, amino group, optionally
20 halogenated alkyl group having 1 to 6 carbon atom(s) (e.g., trifluoromethyl, methyl and the like), alkoxy group having 1 to 6 carbon atom(s) (e.g., methoxy and the like), aromatic heterocyclic group (e.g., quinolyl, thienyl and the like) and cycloalkyl group having 3 to
25 10 carbon atoms (e.g., cyclopentyl and the like).

X is a bond, -O-, -S-, -SO-, -SO₂- or -NR³- (R³ is hydrogen atom or optionally substituted hydrocarbon group).

- Examples of the "optionally substituted hydrocarbon group" for R³ are those exemplified for the aforementioned R⁴ and the like. The "optionally substituted hydrocarbon group" is preferably alkyl group having 1 to 10 carbon atom(s) (e.g., methyl, ethyl and the like) and the like.

- 35 In the formula (I), when X is a bond, R² is preferably an aryl group having 6 to 14 carbon atoms

(e.g., phenyl and the like) optionally having 1 or 2 substituent(s) selected from halogen atom (e.g., fluorine, chlorine and the like), hydroxy group, nitro group, amino group, optionally halogenated alkyl group 5 having 1 to 6 carbon atom(s) (e.g., trifluoromethyl, methyl and the like), alkoxy group having 1 to 6 carbon atom(s) (e.g., methoxy and the like), aromatic heterocyclic group (e.g., quinolyl, thienyl and the like) and cycloalkyl group having 3 to 10 carbon atoms 10 (e.g., cyclopentyl and the like).

In the formula (I), when X is -O-, -S-, -SO-, -SO₂- or -NR³-, R² is preferably an alkyl group having 1 to 10 carbon atom(s) (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, t.-butyl, pentyl and the like) or an aralkyl group having 7 to 13 carbon atoms 15 (e.g., benzyl and the like), each optionally having 1 to 3 (preferably 1 or 2) substituent(s) selected from halogen atom (e.g., fluorine and the like), hydroxy group, nitro group, optionally halogenated alkyl group 20 having 1 to 6 carbon atom(s) (e.g., trifluoromethyl and the like), alkoxy group having 1 to 6 carbon atom(s) (e.g., methoxy and the like), aromatic heterocyclic group (e.g., quinolyl, thienyl and the like) and cycloalkyl group having 3 to 10 substituents (e.g., 25 cyclopentyl and the like).

X is preferably a bond or -O-.

The "divalent hydrocarbon group" for L is, for example,

- (1) C₁₋₁₀ alkylene (e.g., -CH₂-, -(CH₂)₂-, -(CH₂)₃-, -(CH₂)₄-, -(CH₂)₅-, -(CH₂)₆-, -CHCH₃-, -C(CH₃)₂-, -(CH(CH₃))₂-, -(CH₂)₂C(CH₃)₂-, -(CH₂)₃C(CH₃)₂- and the like);
- (2) C₂₋₁₀ alkenylene (e.g., -CH=CH-, -CH₂-CH=CH-, -CH=CH-CH₂-, -CH=CH-CH₂-CH₂-, -C(CH₃)₂-CH=CH-, -CH₂-CH=CH-CH₂-, -CH₂-CH₂-CH=CH-, -CH=CH-CH₂-CH₂-CH=CH- and the like); or

(3) C_{2-10} alkynylene (e.g., $-C\equiv C-$, $-CH_2-C\equiv C-$, $-CH_2-C\equiv C-CH_2-$ CH_2- and the like) and the like.

The "divalent hydrocarbon group" is preferably C_{1-10} alkylene, more preferably $-CH_2-$, $-(CH_2)_2-$ and the like.

5 Particularly, $-CH_2-$ is preferable.

Preferable examples of compound (I) include the following compounds.

[compound A]

A compound wherein ring A is a benzene ring, a 10 naphthalene ring or a thiophene ring, each optionally having 1 or 2 substituent(s) selected from

1) a halogen atom;

2) a nitro group;

3) a cyano group;

15 4) a C_{1-3} alkylenedioxy group;

5) an optionally substituted hydroxy group (preferably methoxy, carbamoylmethoxy and the like);

6) an acyl group (preferably carbamoyl, methoxycarbonyl and the like); and

20 7) an optionally substituted amino group (preferably acetylamino and the like);

R^1 is an alkyl group having 1 to 10 carbon atom(s)

(preferably alkyl group having 4 to 10 carbon atom(s));

R^2 is an alkyl group having 1 to 10 carbon atom(s), an

25 aryl group having 6 to 14 carbon atoms or an aralkyl group having 7 to 13 carbon atoms, each optionally having 1 or 2 substituent(s) selected from halogen atom, hydroxy group, nitro group, optionally halogenated alkyl group having 1 to 6 carbon atom(s), alkoxy group having

30 1 to 6 carbon atom(s), aromatic heterocyclic group (e.g., quinolyl and the like) and cycloalkyl group having 3 to 10 carbon atoms;

X is a bond or $-O-$; and

L is C_{1-10} alkylene.

35 [compound B]

A compound wherein ring A is a benzene ring

optionally having 1 or 2 substituent(s) selected from

- 1) a cyano group;
- 2) a C₁₋₁₀ alkyl group (preferably ethyl) or a C₂₋₁₀ alkenyl group (preferably ethenyl), each optionally
- 5 substituted by carbamoyl group or carboxyl group;
- 3) an optionally substituted hydroxy group [preferably alkoxy group having 1 to 10 carbon atom(s) (preferably methoxy, isopropoxy) optionally having 1 to 3 substituent(s) selected from carbamoyl group, carboxyl
- 10 group and alkoxy carbonyl group having 2 to 5 carbon atoms (preferably methoxycarbonyl); hydroxy group; aralkyloxy group having 7 to 13 carbon atoms (preferably benzyloxy)] [more preferably carbamoylmethoxy];
- 4) an acyl group [preferably C₁₋₆ alkyl-carbonyl (preferably acetyl), carbamoyl, mono- or di-(C₁₋₆ alkyl optionally having 1 to 3 substituent(s) selected from halogen atom and C₁₋₆ alkoxy-carbonyl)-carbamoyl (preferably methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, dimethylcarbamoyl,
- 20 trifluoroethylcarbamoyl, ethoxycarbonylmethylcarbamoyl and the like), C₃₋₁₀ cycloalkyl-carbamoyl (preferably cyclopropylcarbamoyl), C₇₋₁₃ aralkyl-carbamoyl (preferably benzylcarbamoyl), nitrogen-containing heterocycle-carbonyl optionally substituted by hydroxy (preferably pyrrolidinylcarbonyl, piperidinocarbonyl),
- 25 C₁₋₆ alkylsulfonyl (preferably methylsulfonyl), C₁₋₆ alkylsulfinyl (preferably methylsulfinyl), carboxyl, C₁₋₆ alkoxy-carbonyl (preferably methoxycarbonyl), thiocarbamoyl];
- 30 5) an optionally substituted amino group (preferably carbamoylamino);
- 6) an optionally substituted thiol group [preferably alkylthio group having 1 to 10 carbon atom(s) optionally substituted by carbamoyl group (preferably methylthio);
- 35 7) an optionally substituted heterocyclic group [preferably aromatic heterocyclic group (preferably

furyl, thienyl, oxazolyl, oxadiazolyl, thiazolyl, tetrazolyl, pyridyl, pyrrolyl, triazolyl) or non-aromatic heterocyclic group (preferably dioxoisoindole, 5-oxooxadiazol-3-yl, 5-oxothiadiazol-3-yl), each

5 optionally having 1 or 2 substituent(s) selected from C₁₋₆ alkyl group optionally substituted by 1 to 3 halogen atom(s) (preferably methyl, trifluoromethyl), carboxyl group, alkoxy carbonyl group having 2 to 8 carbon atoms (preferably ethoxycarbonyl), cyano group, carbamoyl

10 group, amino group, mono- or di-C₂₋₁₀ alkanoylamino group (e.g., acetyl amino, isopentanoylamino), C₁₋₁₀ alkoxy carbonylamino group (e.g., methoxycarbonylamino), carbamoylamino group, mono- or di-C₁₋₁₀ alkyl-carbamoylamino group (e.g., methylcarbamoylamino,

15 dimethylcarbamoylamino), C₆₋₁₄ aryl-carbonylamino group (e.g., benzoyl amino), C₃₋₁₀ cycloalkyl-carbonylamino group, C₇₋₁₃ aralkyloxy-carbonylamino group, mono- or di-C₁₋₁₀ alkylsulfonylamino group (e.g., methylsulfonylamino, dimethylsulfonylamino), C₆₋₁₄ arylsulfonylamino group and

20 C₁₋₆ alkoxy-carbamoylamino group (e.g., methoxycarbamoylamino); and

8) an amidino group;

R¹ is an alkyl group having 4 to 10 carbon atoms (preferably isobutyl, neopentyl) or a cycloalkylalkyl

25 group having 4 to 10 carbon atoms (preferably cyclopropylmethyl);

R² is an aryl group having 6 to 14 carbon atoms (preferably phenyl) optionally having 1 or 2 substituent(s) selected from halogen atom (preferably

30 fluorine, chlorine) and C₁₋₆ alkyl (preferably methyl); X is a bond; and

L is C₁₋₁₀ alkylene (preferably -CH₂-).

[compound C]

A compound wherein ring A is a benzene ring

35 optionally having 1 or 2 substituent(s) selected from

1) a C₁₋₁₀ alkyl group (preferably ethyl) or a C₂₋₁₀

alkenyl group (preferably ethenyl), each optionally substituted by alkoxy carbonyl group having 2 to 8 carbon atoms (preferably ethoxycarbonyl) or carbamoyl group;

2) an optionally substituted hydroxy group [preferably

5 alkoxy group having 1 to 10 carbon atom(s) (preferably methoxy) optionally substituted by carbamoyl group; more preferably carbamoylmethoxy];

3) an acyl group (preferably carbamoyl, thiocarbamoyl, carboxyl);

10 4) an optionally substituted heterocyclic group [preferably aromatic heterocyclic group (preferably furyl, thienyl, oxazolyl, oxadiazolyl, thiazolyl, tetrazolyl, pyridyl, pyrrolyl, triazolyl) or non-aromatic heterocyclic group (preferably 5-oxooxadiazol-

15 3-yl), each optionally having 1 or 2 substituent(s) selected from C₁₋₆ alkyl group (preferably methyl), carboxyl group, alkoxy carbonyl group having 2 to 8 carbon atoms (preferably ethoxycarbonyl), cyano group, carbamoyl group, amino group, mono- or di-C₂₋₁₀

20 alkanoylamino group (e.g., acetyl amino, isopentanoylamino), C₁₋₁₀ alkoxy-carbonylamino group (e.g., methoxycarbonylamino), carbamoylamino group, mono- or di-C₁₋₁₀ alkyl-carbamoylamino group (e.g., methylcarbamoylamino, dimethylcarbamoylamino), C₆₋₁₄

25 aryl-carbonylamino group (e.g., benzoylamino), C₃₋₁₀ cycloalkyl-carbonylamino group, C₇₋₁₃ aralkyloxy-carbonylamino group, mono- or di-C₁₋₁₀ alkylsulfonylamino group (e.g., methylsulfonylamino, dimethylsulfonylamino), C₆₋₁₄ arylsulfonylamino group and C₁₋₆ alkoxy-

30 carbamoylamino group (e.g., methoxycarbamoylamino)]; R¹ is an alkyl group having 4 to 10 carbon atoms (preferably isobutyl, neopentyl) or a cycloalkylalkyl group having 4 to 10 carbon atom(s) (preferably cyclopropylmethyl);

35 R² is an alkyl group having 1 to 10 carbon atom(s), which is optionally substituted by 1 to 3 halogen

atom(s) (preferably butyl);

X is -O-; and

L is C₁₋₁₀ alkylene (preferably -CH₂-).

Preferable examples of compound (I) include
5 compounds shown by the following formula.

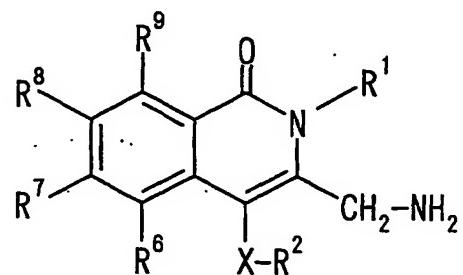


Table 1

No.	X	R ¹	R ²	R ⁶	R ⁷	R ⁸	R ⁹
1	O	neo-Pent	n-Bu	H	Eto-	H	H
2	O	neo-Pent	n-Bu	H	H	F	H
3	O	neo-Pent	n-Bu	H	F	H	H
4	O	Me	Me	H	Cl	H	H
5	O	Me	Me	H	H	Cl	H
6	O	Me	i-Pr	H	Cl	H	H
7	O	Me	n-Bu	H	Cl	H	H
8	O	Me	PhCH ₂ -	H	Cl	H	H
9	O	Me	a)	H	Cl	H	H
10	O	Me	PhCH ₂ CH ₂ -	H	Cl	H	H
11	O	Me	b)	H	Cl	H	H
12	-	Me	Ph	H	H	Cl	H
13	O	Me	n-Pr	H	Cl	H	H
14	O	Me	c)	H	Cl	H	H
15	O	Me	4-NO ₂ Ph	H	Cl	H	H
16	-	Me	4-MeOPh	H	Cl	H	H
17	-	Me	3-MeOPh	H	Cl	H	H
18	-	Me	4-HOPh	H	Cl	H	H
19	-	Me	3-HOPh	H	Cl	H	H
20	-	Me	4-FPh	H	Cl	H	H
21	-	Me	4-F ₃ CPh	H	Cl	H	H
22	-	Me	Ph	H	Cl	Cl	H
23	-	Me	3-NO ₂ Ph	H	Cl	H	H
24	-	Me	3-NH ₂ Ph	H	Cl	H	H
25	O	n-Pr	n-Bu	H	Cl	H	H

Table 2

No.	X	R ¹	R ²	R ⁶	R ⁷	R ⁸	R ⁹
26	O	i-Bu	n-Bu	H	Cl	Cl	H
27	O	neo-Pent	n-Bu	H	Cl	Cl	H
28	O	PhCH ₂ -	n-Bu	H	Cl	Cl	H
29	O	i-Bu	n-Pent	H	Cl	Cl	H
30	O	i-Pr	n-Bu	H	Cl	Cl	H
31	O	c-Pr	n-Bu	H	Cl	Cl	H
32	O	c-PrCH ₂ -	n-Bu	H	Cl	Cl	H
33	O	i-Pent	n-Bu	H	Cl	Cl	H
34	O	neo-Pent	i-Bu	H	Cl	Cl	H
35	O	d)	n-Bu	H	Cl	Cl	H
36	O	Me	n-Bu	H	Cl	Cl	H
41	O	e)	n-Bu	H	Cl	Cl	H
42	O	f)	n-Bu	H	Cl	Cl	H
43	O	g)	n-Bu	H	Cl	Cl	H
44	O	h)	n-Bu	H	Cl	Cl	H
45	O	i)	n-Bu	H	Cl	Cl	H
46	O	neo-Pent	n-Bu	H	H	H	H
47	O	j)	n-Bu	H	Cl	Cl	H
48	O	MeOCH ₂ CH ₂ -	n-Bu	H	Cl	Cl	H
49	O	neo-Pent	MeOCH ₂ CH ₂ -	H	H	H	H
50	O	neo-Pent	n-Bu	H	H	Me	H

Table 3

No.	X	R ¹	R ²	R ⁶	R ⁷	R ⁸	R ⁹
51	O	neo-Pent	n-Bu	H	Me	H	H
52	O	neo-Pent	n-Bu	H	H	CF ₃	H
53	O	neo-Pent	n-Bu	H	CF ₃	H	H
54	O	k)	n-Bu	H	Cl	Cl	H
55	O	l)	n-Bu	H	Cl	Cl	H
57	O	neo-Pent	n-Bu	H	MeO-	H	H
58	O	neo-Pent	n-Bu	H	PhCH ₂ O-	H	H
59	O	neo-Pent	n-Bu	H	HO-	H	H
60	O	neo-Pent	n-Bu	H	n-PrO-	H	H
61	O	neo-Pent	n-Bu	H	n-BuO-	H	H
62	O	neo-Pent	n-Bu	H	MeOCH ₂ CH ₂ O-	H	H
63	O	neo-Pent	n-Bu	H	H	PhCH ₂ O	H
64	O	neo-Pent	n-Bu	H	H	HO-	H
65	O	neo-Pent	n-Bu	H	H	MeO-	H
66	O	neo-Pent	n-Bu	H	H	EtO-	H
67	O	neo-Pent	n-Bu	H	H	n-PrO	H
68	O	neo-Pent	n-Bu	H	H	n-BuO	H
69	O	neo-Pent	n-Bu	MeO	MeO-	H	H
70	O	neo-Pent	n-Bu	H	MeO-	MeO-	H
74	O	i-Bu	n-Bu	H	Br	H	H
75	O	i-Bu	n-Bu	H	MeOCO-	H	H

Table 4

No.	X	R ¹	R ²	R ⁶	R ⁷	R ⁸	R ⁹
76	O	i-Bu	n-Bu	H	HOCO—	H	H
77	O	i-Bu	n-Bu	H	H ₂ NCO—	H	H
78	O	i-Bu	n-Bu	H	NC—	H	H
79	O	i-Bu	n-Bu	H	HOCH ₂ —	H	H
80	O	i-Bu	n-Bu	H	MeNHCONH—	H	H
81	O	i-Bu	n-Bu	H	MeOCONH—	H	H
82	O	i-Bu	n-Bu	H	NH ₂ —	H	H
83	O	neo-Pent	n-Bu	H	Br	H	H
84	O	neo-Pent	n-Bu	H	MeOCO—	H	H
85	O	neo-Pent	n-Bu	H	HOCO—	H	H
86	O	neo-Pent	n-Bu	H	H ₂ NCO—	H	H
87	O	neo-Pent	n-Bu	H	NC—	H	H
88	O	i-Bu	n-Bu	H	AcNH—	H	H
89	O	i-Bu	n-Bu	H	EtCONH—	H	H
90	O	i-Bu	n-Bu	H	m)	H	H
91	O	i-Bu	n-Bu	H	n)	H	H
92	O	i-Bu	n-Bu	H	o)	H	H
93	O	i-Bu	n-Bu	H	MsNH—	H	H
94	O	i-Bu	n-Bu	H	PhSO ₂ NH—	H	H
95	O	neo-Pent	n-Bu	H	p)	H	H
96	O	neo-Pent	n-Bu	H	i-PrO—	H	H
97	O	neo-Pent	n-Bu	H	CF ₃ CH ₂ O—	H	H
98	O	neo-Pent	n-Bu	H	q)	H	H
99	O	neo-Pent	n-Bu	H	r)	H	H
100	O	neo-Pent	n-Bu	H	i-BuO—	H	H

Table 5

No.	X	R ¹	R ²	R ⁶	R ⁷	R ⁸	R ⁹
101	O	neo-Pent	n-Bu	H	s)	H	H
102	O	neo-Pent	n-Bu	H	t)	H	H
103	O	neo-Pent	n-Bu	H	u)	H	H
104	O	neo-Pent	n-Bu	H	EtOCOCH ₂ O-	H	H
105	O	neo-Pent	n-Bu	H	v)	H	H
106	-	i-Bu	Ph	H	Br	H	H
107	-	i-Bu	Ph	H	MeOCO-	H	H
108	-	i-Bu	Ph	H	HOCO-	H	H
109	-	i-Bu	Ph	H	H ₂ NCO-	H	H
110	-	i-Bu	Ph	H	CbzNH-	H	H
111	-	i-Bu	Ph	H	NH ₂ -	H	H
112	-	i-Bu	Ph	H	AcNH-	H	H
113	-	Et	Ph	H	Cl	H	H
114	-	n-Pr	Ph	H	Cl	H	H
115	-	n-Bu	Ph	H	Cl	H	H
116	-	Me	Ph	H	Br	H	H
117	-	n-Pent	Ph	H	Cl	H	H
118	-	i-Bu	Ph	H	Cl	H	H
119	-	C-HexCH ₂ -	Ph	H	Cl	H	H
120	-	i-Bu	4-FPh	H	Cl	Cl	H
121	-	i-Bu	Ph	H	Cl	Cl	H
122	-	neo-Pent	Ph	H	Cl	H	H
123	-	i-Bu	Ph	H	H	H	H
124	-	i-Bu	4-ClPh	H	H	H	H
125	-	i-Bu	4-MePh	H	H	H	H

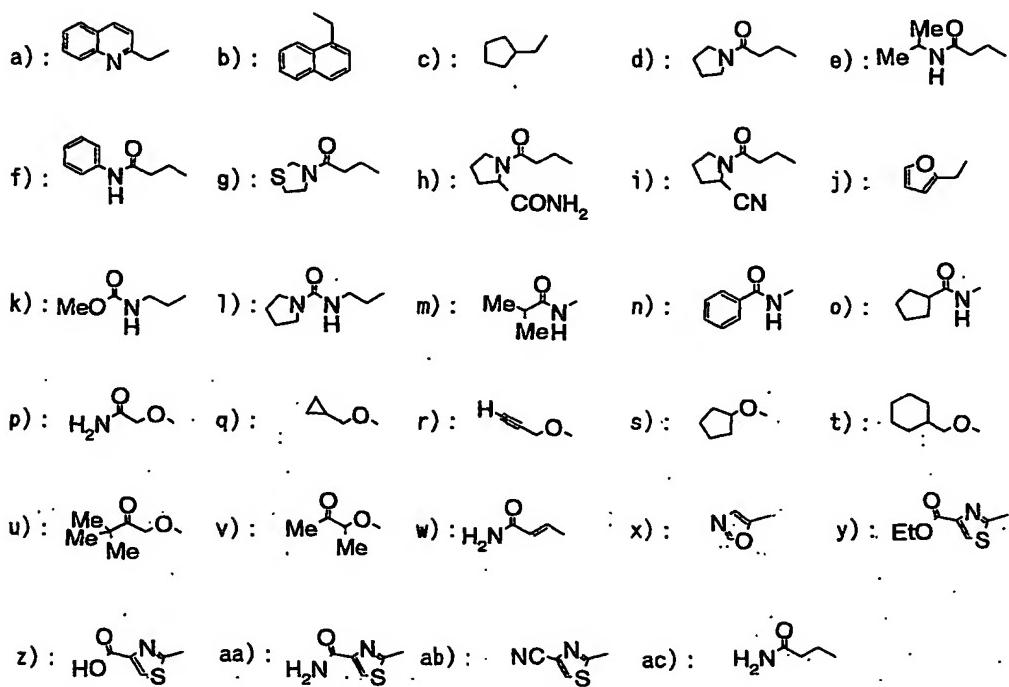
Table 6

No.	X	R ¹	R ²	R ⁶	R ⁷	R ⁸	R ⁹
126	-	i-Bu	Ph	H	F	H	H
127	-	i-Bu	Ph	H	MeO-	H	H
128	-	i-Bu	Ph	H	EtO-	H	H
129	-	i-Bu	Ph	H	n-PrO-	H	H
130	-	i-Bu	Ph	H	MeO-	MeO-	H
131	-	i-Bu	4-FPh	H	MeOCO-	H	H
132	-	i-Bu	4-FPh	H	HOCO-	H	H
133	-	i-Bu	4-FPh	H	H ₂ NCO-	H	H
134	-	i-Bu	4-FPh	H	AcNH-	H	H
135	-	i-Bu	4-FPh	H	EtO-	H	H
136	-	i-Bu	4-FPh	H	p)	H	H
137	-	i-Bu	2-FPh	H	MeOCO-	H	H
138	-	i-Bu	2-FPh	H	HOCO-	H	H
139	-	i-Bu	2-FPh	H	H ₂ NCO-	H	H
140	-	i-Bu	2-FPh	H	AcNH-	H	H
141	-	i-Bu	2-FPh	H	p)	H	H
142	-	i-Bu	3-FPh	H	MeOCO-	H	H
143	-	i-Bu	3-FPh	H	HOCO-	H	H
144	-	i-Bu	3-FPh	H	H ₂ NCO-	H	H
145	-	i-Bu	3-FPh	H	AcNH-	H	H
146	-	i-Bu	3-FPh	H	EtO-	H	H
147	-	i-Bu	Ph	H	MeNHCONH-	H	H
148	-	i-Bu	Ph	H	Me ₂ NCONH-	H	H
149	-	i-Bu	Ph	H	H ₂ NCONH-	H	H
150	O	i-Bu	CF ₃ CH ₂ CH ₂ CH ₂ -	H	p)	H	H

Table 7

No.	X	R ¹	R ²	R ⁶	R ⁷	R ⁸	R ⁹
151	O	c-PrCH ₂ -	n-Bu	H	H ₂ NCO-	H	H
152	O	c-PrCH ₂ -	n-Bu	H	p)	H	H
153	O	c-PrCH ₂ -	n-Bu	H	w)	H	H
154	O	i-Bu	n-Bu	H	p)	H	H
155	O	i-Bu	n-Bu	H	w)	H	H
156	-	i-Bu	Ph	H	NC-	H	H
157	-	i-Bu	Ph	H	MeNHCO-	H	H
158	-	i-Bu	Ph	H	p)	H	H
159	-	i-Bu	Ph	H	w)	H	H
160	O	neo-Pent	n-Bu	H	w)	H	H
161	O	c-PrCH ₂ -	n-Bu	H	x)	H	H
162	O	i-Bu	n-Bu	H	x)	H	H
163	-	i-Bu	Ph	H	x)	H	H
164	O	i-Bu	n-Bu	H	y)	H	H
165	-	i-Bu	Ph	H	y)	H	H
166	O	i-Bu	n-Bu	H	z)	H	H
167	-	i-Bu	Ph	H	z)	H	H
168	O	i-Bu	n-Bu	H	aa)	H	H
169	-	i-Bu	Ph	H	aa)	H	H
170	O	i-Bu	n-Bu	H	ab)	H	H
171	-	i-Bu	Ph	H	ab)	H	H
172	-	i-Bu	4-MePh	H	p)	H	H
173	-	i-Bu	4-ClPh	H	p)	H	H
174	-	i-Bu	4-MePh	H	z)	H	H
175	-	i-Bu	4-ClPh	H	z)	H	H
176	-	i-Bu	4-MePh	H	ac)	H	H

The symbols in the Tables mean the following:



5

Me: methyl, Et: ethyl, CF₃: trifluoromethyl,
 neo-Pent: neopentyl, n-Bu: n-butyl, i-Bu: isobutyl,
 i-Pr: isopropyl, Ph: phenyl, n-Pr: n-propyl,
 4-NO₂Ph: 4-nitrophenyl, 4-MeOPh: 4-methoxyphenyl,
 10 4-MePh: 4-methylphenyl, 4-HOPh: 4-hydroxyphenyl,
 3-MeOPh: 3-methoxyphenyl, 3-HOPh: 3-hydroxyphenyl,
 4-FPh: 4-fluorophenyl, 4-CF₃Ph: 4-trifluoromethylphenyl,
 3-NO₂Ph: 3-nitrophenyl, 3-NH₂Ph: 3-aminophenyl,
 n-Pent: n-pentyl, i-Pent: isopentyl, c-Pr:
 15 cyclopropyl,
 c-Hex: cyclohexyl, 4-ClPh: 4-chlorophenyl,
 2-FPh: 2-fluorophenyl, 3-FPh: 3-fluorophenyl,
 Cbz: benzyloxycarbonyl, Ac: acetyl, Ms:

methanesulfonyl

More Preferable examples of compound (I) include:

- 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-1,3-thiazole-4-carbonitrile;
- 5 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-1,3-thiazole-4-carboxylic acid;
- 10 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-1,3-thiazole-4-carboxamide;
- 15 ethyl 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-1,3-thiazole-4-carboxylate;
- (E)-3-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-2-propenamide;
- (E)-3-[3-(aminomethyl)-2-isobutyl-4-phenyl-1-oxo-1,2-dihydro-6-isoquinolyl]-2-propenamide;
- 20 3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinecarboxamide;
- 25 2-[[3-(aminomethyl)-2-isobutyl-4-phenyl-1-oxo-1,2-dihydro-6-isoquinolyl]oxy]acetamide; and the like.

As a salt of the compound of the formula (I)

- 20 (hereinafter sometimes to be abbreviated as compound (I)), pharmaceutically acceptable salt is preferable. Examples of such salt include salt with inorganic base; salt with organic base, salt with inorganic acid; salt with organic acid, salt with basic or acidic amino acid
- 25 and the like.

Preferable examples of the salt with inorganic base include alkali metal salts such as sodium salt, potassium salt and the like; alkaline earth metal salts such as calcium salt, magnesium salt and the like;

- 30 aluminum salt; ammonium salt and the like.

Preferable examples of the salt with organic base include a salt with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N-

- 35 dibenzylethylenediamine or the like.

Preferable examples of the salt with inorganic acid

include a salt with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid or the like.

Preferable examples of the salt with organic acid include a salt with formic acid, acetic acid,

- 5 trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid or the like.

- Preferable examples of the salt with basic amino acid include a salt with arginine, lysin, ornithine or the like.

Preferable examples of the salt with acidic amino acid include a salt with aspartic acid, glutamic acid or the like.

- 15 Of the above-mentioned salts, sodium salt, potassium salt, hydrochloride and the like are preferable.

A prodrug of compound (I) is a compound that converts to compound (I) due to the reaction of enzyme,

- 20 gastric acid and the like under the physiological conditions in the body. That is, a compound that converts to compound (I) by enzymatic oxidation, reduction, hydrolysis and the like, and a compound that converts to compound (I) by hydrolysis and the like by 25 gastric acid and the like. A prodrug of compound (I) is exemplified by a compound wherein an amino group of compound (I) is acylated, alkylated, phosphorylated (e.g., compound where amino group of compound (I) is eicosanoylated, alanylated, pentylaminocarbonylated, (5-30 methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylated, tetrahydrofurylated, pyrrolidylmethylated, pivaloyloxymethylated, tert-butylated and the like); compound wherein a hydroxy group of compound (I) is acylated, alkylated, phosphorinated, borated (e.g., 35 compound where hydroxy group of compound (I) is acetylated, palmitoylated, propanoylated, pivaloylated,

succinilated, fumarinated, alanilated,
dimethylaminomethylcarbonylated and the like); compound
wherein a carboxyl group of compound (I) is esterified
or amidated (e.g., compound where carboxyl group of
5 compound (I) is ethyl esterified, phenyl esterified,
carboxymethyl esterified, dimethylaminomethyl esterified,
pivaloyloxymethyl esterified, ethoxycarbonyloxyethyl
esterified, phthalidyl esterified, (5-methyl-2-oxo-1,3-
dioxolen-4-yl)methyl esterified,
10 cyclohexyloxycarbonyethyl esterified, methylamidated and
the like) and the like. These compounds can be produced
from compound (I) by a method known *per se*.

A prodrug of compound (I) may be a compound that
converts to compound (I) under physiological conditions
15 as described in Development of pharmaceutical products,
vol. 7, Molecule Design, 163-198, Hirokawa Shoten (1990).

The compound (I) may be labeled with isotope (e.g.,
³H, ¹⁴C, ³⁵S, ¹²⁵I and the like) and the like.

The compound (I) may be an anhydride or a hydrate.
20 The compound (I), a salt thereof and a prodrug
thereof (hereinafter sometimes to be simply referred to
as the compound of the present invention) show low
toxicity and can be used as an agent for the prophylaxis
or treatment of various diseases to be mentioned later
25 for mammal (e.g., human, mouse, rat, rabbit, dog, cat,
cattle, horse, swine, simian and the like) by admixing
with a pharmacologically acceptable carrier and the like
to give a pharmaceutical composition.

Here, various organic or inorganic carriers
30 conventionally used as materials for pharmaceutical
preparations are used as a pharmacologically acceptable
carrier, which are added as excipient, lubricant, binder,
disintegrant for solid preparations; and solvent,
dissolution aids, suspending agent, isotonicity agent,
35 buffer, soothing agent and the like for liquid
preparations. Where necessary, additive for

pharmaceutical preparations such as preservative, antioxidant, coloring agent, sweetening agent and the like can be used.

Preferable examples of the excipient include

- 5 lactose, sucrose, D-mannitol, D-sorbitol, pregelatinized starch, dextrin, crystalline cellulose, low-substituted hydroxypropylcellulose, sodium carboxymethylcellulose, gum arabic, dextrin, pullulan, light silicic anhydride, synthetic aluminum silicate, magnesium aluminate
- 10 metasilicate and the like.

Preferable examples of the lubricant include magnesium stearate, calcium stearate, talc, colloidal silica and the like.

Preferable examples of the binder include

- 15 pregelatinized starch, saccharose, gelatin, gum arabic, methylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose, crystalline cellulose, sucrose, D-mannitol, trehalose, dextrin, pullulan, hydroxypropyl cellulose, hydroxypropylmethylcellulose,
- 20 polyvinylpyrrolidone and the like.

Preferable examples of the disintegrant include lactose, sucrose, starch, carboxymethylcellulose, calcium carboxymethylcellulose, sodium crosscarmellose, sodium carboxymethyl starch, light silicic anhydride, 25 low-substituted hydroxypropylcellulose and the like.

Preferable examples of the solvent include water for injection, physiological brine, Ringer's solution, alcohol, propylene glycol, polyethylene glycol, sesame oil, corn oil, olive oil, cottonseed oil and the like.

- 30 Preferable examples of the dissolution aids include polyethylene glycol, propylene glycol, D-mannitol, trehalose, benzyl benzoate, ethanol, Tris aminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate, sodium salicylate, sodium acetate and the like.

- 35 Preferable examples of the suspending agent include surfactants such as stearyltriethanolamine, sodium

lauryl sulfate, lauryl aminopropionate, lecithin, benzalkonium chloride, benzethonium chloride, monostearic glyceride and the like; hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, sodium 5 carboxymethylcellulose, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and the like; polysorbates, polyoxyethylene hydrogenated castor oil and the like.

Preferable examples of the isotonicity agent 10 include sodium chloride, glycerol, D-mannitol, D-sorbitol, glucose and the like.

Preferable examples of the buffer include phosphate buffer, acetate buffer, carbonate buffer, citrate buffer, and the like.

15 Preferable examples of the soothing agent include benzyl alcohol and the like.

Preferable examples of the preservative include p-oxybenzoic acid esters, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, sorbic acid and 20 the like.

Preferable examples of the antioxidant include sulfite, ascorbate and the like.

25 Preferable examples of the coloring agent include water-soluble edible tar pigment (e.g., foodcolors such as Food Color Red Nos. 2 and 3, Food Color Yellow Nos. 4 and 5, Food Color Blue Nos. 1 and 2 and the like, water insoluble lake pigment (e.g., aluminum salt of the aforementioned water-soluble edible tar pigment and the like), natural pigments (e.g., beta carotene, chlorophil, red iron oxide etc.) and the like.

Preferable examples of the sweetening agent include saccharin sodium, dipotassium glycyrrhizinate, aspartame, stevia and the like.

The dosage form of the aforementioned 35 pharmaceutical composition may be, for example, oral agents such as tablets (inclusive of sublingual tablets

and orally disintegrable tablets), capsules (inclusive of soft capsules and micro capsules), granules, powders, troches, syrups, emulsions, suspensions and the like; or parenteral agents such as injections (e.g., subcutaneous 5 injections, intravenous injections, intramuscular injections, intraperitoneal injections, drip infusions and the like), external agents (e.g., transdermal preparations, ointments and the like), suppositories (e.g., rectal suppositories, vaginal suppositories and 10 the like), pellets; nasal preparations, pulmonary preparations (inhalations), ophthalmic preparations and the like. These may be administered safely via oral or parenteral route. These agents may be controlled-release preparations such as rapid-release preparations. 15 and sustained-release preparations (e.g., sustained-release microcapsules).

The pharmaceutical composition can be produced according to a method conventionally used in the field of pharmaceutical preparation, such as the method 20 described in Japan Pharmacopoeia and the like. The specific production methods of the pharmaceutical preparation are described in detail in the following.

While the content of the compound of the present invention in the pharmaceutical composition varies 25 depending on dosage form, dose of the compound of the present invention and the like, it is, for example, about 0.1-100 wt%.

For example, an oral agent is produced by adding, to the active ingredient, excipient (e.g., lactose, 30 sucrose, starch, D-mannitol and the like), disintegrant (e.g., calcium carboxymethylcellulose and the like), binder (e.g., pregelatinated starch, gum arabic, carboxymethylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone and the like), lubricant (e.g., 35 talc, magnesium stearate, polyethylene glycol 6000 and the like) and the like, compression-shaping the mixture,

and where necessary, coating the same using a coating base for masking of taste, enteric property or sustained release according to a method known per se.

Examples of the coating base include a sugar-
5 coating base, a water-soluble film coating base, an enteric film coating base, a sustained release film coating base and the like.

As a sugar-coating base, sucrose may be used, along with one or two species selected from talc, precipitated
10 calcium carbonate, gelatin, gum arabic, pullulan, carnauba wax and the like.

As a water-soluble film coating base, for example, cellulose polymers such as hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose,
15 methylhydroxyethylcellulose and the like; synthetic polymers such as polyvinyl acetal diethylaminoacetate, aminoalkyl methacrylate copolymer E [Eudragit E, trademark, Rohm Pharma], polyvinylpyrrolidone and the like; polysaccharides such as pullulan and the like; and
20 the like are used.

As a enteric film coating base, for example, cellulose polymers such as hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate, carboxymethylethylcellulose, acetic phthalic
25 cellulose and the like; acrylic acid polymers such as methacrylic acid copolymer L [Eudragit L, trademark, Rohm Pharma], methacrylic acid copolymer LD [Eudragit L-30D55, trademark, Rohm Pharma], methacrylic acid copolymer S [Eudragit S, trademark, Rohm Pharma] and the like; naturally occurring substance such as shellac and the like; and the like are used.

As a sustained release film coating base, for example, cellulose polymers such as ethylcellulose and the like; acrylic acid polymers such as aminoalkyl
35 methacrylate copolymer RS [Eudragit RS, trademark, Rohm Pharma], ethyl acrylate-methyl methacrylate copolymer

suspension [Eudragit NE, trademark, Rohm Pharma] and the like, and the like are used.

Two or more kinds of the above-mentioned coating bases may be mixed in an appropriate ratio for use. In addition, a light shielding agent such as titanium oxide, iron tri or dioxide and the like may be used during coating.

An injection is produced by dissolving, suspending or emulsifying an active ingredient in an aqueous solvent (e.g., distilled water, physiological saline, Ringer's solution and the like) or an oily solvent (e.g., plant oil such as olive oil, sesame oil, cottonseed oil, corn oil and the like, propylene glycol and the like) and the like, together with a dispersing agent (e.g., polysorbate 80, polyoxyethylene hydrogenated castor oil 60 and the like), polyethylene glycol, carboxymethylcellulose, sodium alginate and the like), preservative (e.g., methylparaben, propylparaben, benzyl alcohol, chlorobutanol, phenol and the like), isotonicity agent (e.g., sodium chloride, glycerol, D-mannitol, D-sorbitol, glucose and the like) and the like. In this step, dissolution aids (e.g., sodium salicylate, sodium acetate and the like), stabilizers (e.g., human serum albumin and the like), soothing agents (e.g., benzyl alcohol and the like) and the like may be used on demand.

The compound of the present invention and the pharmaceutical agent of the present invention show low toxicity, cause fewer side effects and can be used as an agent for the prophylaxis or treatment or diagnosis of various diseases to be mentioned later for mammal (e.g., human, cattle, horse, dog, cat, simian, mouse, rat, especially human).

The compound of the present invention and the pharmaceutical agent of the present invention have a superior peptidase inhibitory activity and can suppress

peptidase-caused degradation of a physiologically active substance such as peptide hormones, cytokines, neurotransmitters and the like.

Examples of the peptide hormones include glucagon-like peptide-1 (GLP-1), glucagon-like peptide-2 (GLP-2), GIP, growth hormone release hormone (GHRH) and the like.

Examples of the cytokines include chemokine such as RANTES and the like.

Examples of the neurotransmitters include neuropeptide Y and the like.

Examples of the peptidase include EC 3.4.11.1 (Leucyl aminopeptidase), EC 3.4.11.2 (Membrane alanine aminopeptidase), EC 3.4.11.3 (Cystinyl aminopeptidase), EC 3.4.11.4 (Tripeptide aminopeptidase), EC 3.4.11.5 (Prolyl aminopeptidase), EC 3.4.11.6 (Aminopeptidase B), EC 3.4.11.7 (Glutamyl aminopeptidase), EC 3.4.11.9 (Xaa-Pro aminopeptidase), EC 3.4.11.10 (Bacterial leucyl aminopeptidase), EC 3.4.11.13 (Clostridial aminopeptidase), EC 3.4.11.14 (Cytosol alanyl aminopeptidase), EC 3.4.11.15 (Lysyl aminopeptidase), EC 3.4.11.16 (Xaa-Trp aminopeptidase), EC 3.4.11.17 (Tryptophanyl aminopeptidase), EC 3.4.11.18 (Methionyl aminopeptidase), EC 3.4.11.19 (D-stereospecific aminopeptidase), EC 3.4.11.20 (Aminopeptidase Ey), EC 3.4.11.21 (Aspartyl aminopeptidase), EC 3.4.11.22 (Aminopeptidase I), EC 3.4.13.3 (Xaa-His dipeptidase), EC 3.4.13.4 (Xaa-Arg dipeptidase), EC 3.4.13.5 (Xaa-methyl-His dipeptidase), EC 3.4.13.7 (Glu-Glu dipeptidase), EC 3.4.13.9 (Xaa-Pro dipeptidase), EC 3.4.13.12 (Met-Xaa dipeptidase), EC 3.4.13.17 (Non-stereospecific dipeptidase), EC 3.4.13.18 (Cytosol nonspecific dipeptidase), EC 3.4.13.19 (Membrane dipeptidase), EC 3.4.13.20 (Beta-Ala-His dipeptidase), EC 3.4.14.1 (Dipeptidyl-peptidase I), EC 3.4.14.2 (Dipeptidyl-peptidase II), EC 3.4.14.4 (Dipeptidyl-peptidase III), EC 3.4.14.5 (Dipeptidyl-peptidase IV),

EC 3.4.14.6 (Dipeptidyl-dipeptidase), EC 3.4.14.9 (Tripeptidyl-peptidase I), EC 3.4.14.10 (Tripeptidyl-peptidase II) and EC 3.4.14.11 (Xaa-Pro dipeptidyl-peptidase) as classified by International Union of

- 5 Biochemistry and Molecular Biology (IUBMB), and the like. Of these, EC 3.4.14.1, EC 3.4.14.2, EC 3.4.14.4, EC 3.4.14.5, EC 3.4.14.6, EC 3.4.14.9, EC 3.4.14.10 and EC 3.4.14.11 are preferable. Especially preferred is EC 3.4.14.5.

- 10 The compound of the present invention and the pharmaceutical agent of the present invention are useful as a prophylactic and therapeutic agent of diabetes (e.g., type 1 diabetes, type 2 diabetes, gestational diabetes and the like); prophylactic and therapeutic agent of hyperlipidemia (e.g., hypertriglyceridemia, hypercholesterolemia, low HDL lipemia, postprandial lipemia and the like); prophylactic and therapeutic agent of arteriosclerosis; prophylactic and therapeutic agent of impaired glucose tolerance [IGT]; an insulin secretagogue; and an agent for suppressing progress of impaired glucose tolerance into diabetes.

For diagnostic criteria of diabetes, Japan Diabetes Society reported new diagnostic criteria in 1999.

According to this report, diabetes is a condition showing any of a fasting blood glucose level (glucose concentration of intravenous plasma) of not less than 126 mg/dl, a 75 g oral glucose tolerance test (75 g OGTT) 2 h level (glucose concentration of intravenous plasma) of not less than 200 mg/dl, a non-fasting blood glucose level (glucose concentration of intravenous plasma) of not less than 200 mg/dl. A condition not falling under the above-mentioned diabetes, or "a condition showing a fasting blood glucose level (glucose concentration of intravenous plasma) of less than 110 mg/dl or a 75 g oral glucose tolerance test (75 g OGTT) 2 h level (glucose concentration of intravenous plasma)

of less than 140 mg/dl" (normal type) is called a "borderline type".

In addition, ADA (American Diabetes Academy) reported new diagnostic criteria of diabetes in 1997 and 5 WHO in 1998.

According to these reports, diabetes is a condition showing a fasting blood glucose level (glucose concentration of intravenous plasma) of not less than 126 mg/dl and a 75 g oral glucose tolerance test 2 h 10 level (glucose concentration of intravenous plasma) of not less than 200 mg/dl.

According to the above-mentioned reports, impaired glucose tolerance is a condition showing a fasting blood glucose level (glucose concentration of intravenous plasma) of less than 126 mg/dl and a 75 g oral glucose tolerance test 2 h 15 level (glucose concentration of intravenous plasma) of not less than 140 mg/dl and less than 200 mg/dl. According to the report of ADA, a condition showing a fasting blood glucose level (glucose concentration of intravenous plasma) of not less than 20 110 mg/dl and less than 126 mg/dl is called IFG (Impaired Fasting Glucose). According to the report of WHO, among the IFG (Impaired Fasting Glucose), a condition showing a 75g oral glucose tolerance test 2 h 25 level (glucose concentration of intravenous plasma) of less than 140 mg/dl is called IFG (Impaired Fasting Glycemia).

The compound of the present invention and the pharmaceutical agent of the present invention can be 30 also used as a prophylactic and therapeutic agent of diabetes, borderline type, impaired glucose tolerance, IFG (Impaired Fasting Glucose) and IFG (Impaired Fasting Glycemia), as determined according to the above-mentioned new diagnostic criteria. Moreover, the 35 compound of the present invention and the pharmaceutical agent of the present invention can prevent progress of

borderline type, impaired glucose tolerance, IFG (Impaired Fasting Glucose) or IFG (Impaired Fasting Glycemia) into diabetes.

The compound of the present invention and the pharmaceutical agent of the present invention can be also used as a prophylactic and therapeutic agent of, for example, diabetic complications [e.g., neuropathy, nephropathy, retinopathy, cataract, macroangiopathy, osteopenia, hyperosmolar diabetic coma, infectious disease (respiratory infection, urinary tract infection, gastrointestinal infection, dermal soft tissue infections, inferior limb infection and the like), diabetic gangrene, xerostomia, hypacusis, cerebrovascular disorder, peripheral blood circulation disorder and the like], obesity, osteoporosis, cachexia (e.g., cancerous cachexia, tuberculous cachexia, diabetic cachexia, blood disease cachexia, endocrine disease cachexia, infectious disease cachexia or cachexia due to acquired immunodeficiency syndrome), fatty liver, hypertension, polycystic ovary syndrome, kidney disease (e.g., diabetic nephropathy, glomerular nephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, end stage kidney disease and the like), muscular dystrophy, myocardial infarction, angina pectoris, cerebrovascular accident (e.g., cerebral infarction, cerebral apoplexy), insulin resistance syndrome, Syndrome X, hyperinsulinemia, hyperinsulinemia-induced sensory disorder, tumor (e.g., leukemia, breast cancer, prostatic cancer, skin cancer and the like), irritable bowel syndrome, acute or chronic diarrhea, inflammatory diseases (e.g., chronic rheumatoid arthritis, spondylitis deformans, arthritis deformans, lumbar pain, gout, postoperative or traumatic inflammation, remission of tumentia, neuralgia, pharyngolaryngitis, cystitis, hepatitis (inclusive of nonalcoholic steatohepatitis), pneumonia, pancreatitis,

inflammatory bowel disease, ulcerative colitis, gastric mucosal injury (inclusive of gastric mucosal injury caused by aspirin) and the like), visceral obesity syndrome and the like.

5 The compound of the present invention and the pharmaceutical agent of the present invention can be also used for decreasing visceral fat, suppressing visceral fat accumulation, improving glycometabolism, improving lipid metabolism, suppressing production of
10 oxidized LDL, improving lipoprotein metabolism, improving coronary artery metabolism, prophylaxis and treatment of cardiovascular complication, prophylaxis and treatment of heart failure complication, lowering blood remnant, prophylaxis and treatment of anovulation,
15 prophylaxis and treatment of hypertrichosis, prophylaxis and treatment of hyperandrogenemia, improving pancreatic (β cell) function, regeneration of pancreatic (β cell), promotion of pancreatic (β cell) regeneration, and the like.

20 The compound of the present invention and the pharmaceutical agent of the present invention can be also used for secondary prophylaxis and suppression of progression of the above-mentioned various diseases (e.g., cardiovascular event such as myocardial
25 infarction and the like).

 The compound of the present invention and the pharmaceutical agent of the present invention is a glucose dependent insulin secretagogue that selectively promotes insulin secretion in hyperglycemic patients
30 (e.g., patients showing fasting blood glucose level of not less than 126 mg/dl or 75 g oral glucose tolerance test (75 g OGTT) 2 h level of not less than 140 mg/dl and the like). Therefore, the compound of the present invention and the pharmaceutical agent of the present
35 invention are useful as a safe prophylactic or therapeutic agent of diabetes with a low risk of

vascular complications, hypoglycemia induction and the like caused by insulin.

While the dose of the compound of the present invention and the pharmaceutical agent of the present invention varies depending on the administration subject, administration route, target disease, condition and the like, the compound of the present invention as an active ingredient is generally given in a single dose of about 0.01-100 mg/kg body weight, preferably 0.05-30 mg/kg body weight, more preferably 0.1-10 mg/kg body weight, in the case of, for example, oral administration to adult diabetic patients. This dose is desirably given 1 to 3 times a day.

The compound of the present invention can be used in combination with therapeutic agents such as a therapeutic agent of diabetes, a therapeutic agent of diabetic complications, an antihyperlipemia agent, an antihypertensive agent, an antiobestic agent, a diuretic, a chemotherapeutic agent, an immunotherapeutic agent, an antithrombotic agent, a therapeutic agent of osteoporosis, an antidementia agent, an agent for the improvement of erectile dysfunction, a therapeutic agent of incontinentia or pollakiuria and the like (hereinafter to be referred to as a combination drug).

In this case, the timing of administration of the compound of the present invention and a combination drug is not limited. These may be simultaneously administered to an administration object or administered in a staggered manner. Moreover, the compound of the present invention and a combination drug may be administered as two kinds of preparations each containing an active ingredient, or may be administered as a single preparation containing both active ingredients.

The dose of the combination drug can be determined as appropriate based on the dose clinically employed.

The proportion of the compound of the present invention and combination drug can be appropriately determined depending on the administration subject, administration route, target disease, condition, combination and the like. When, for example, the administration subject is human, a combination drug is used in an amount of 0.01-100 parts by weight per 1 part by weight of the compound of the present invention.

- Examples of the therapeutic agent of diabetes include insulin preparations (e.g., animal insulin preparations extracted from pancreas of cattle, swine; human insulin preparations synthesized by genetic engineering techniques using *Escherichia coli* or yeast; zinc insulin; protamine zinc insulin; fragments or derivatives of insulin (e.g., INS-1 and the like) and the like), insulin sensitizers (e.g., pioglitazone hydrochloride, rosiglitazone (maleate), GI-262570, JTT-501, MCC-555, YM-440, KRP-297, CS-011, FK-614, NN-622, AZ-242, BMS-298585, EML-16336, compounds described in WO99/58510 (e.g., (E)-4-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzyloxyimino]-4-phenylbutyric acid) and the like), PPAR γ agonists, PPAR γ antagonists, PPAR γ/α dual agonists, α -glucosidase inhibitors (e.g., voglibose, acarbose, miglitol, emiglitate and the like), biguanides (e.g., phenformin, metformin, buformin and the like), insulin secretagogues [sulfonylureas (e.g., tolbutamide, glibenclamide, gliclazide, chlorpropamide, tolazamide, acetohexamide, glyclopypamide, glimepiride, glipizide, glybzazole and the like), repaglinide, senaglinide, nateglinide, mitiglinide or calcium salt hydrate thereof], GLP-1 receptor agonists [e.g., GLP-1, NN-2211, AC-2993 (exendin-4), BIM-51077, Aib(8,35)hGLP-1(7,37)NH₂ and the like], amylin agonists (e.g., pramlintide and the like), phosphotyrosine phosphatase inhibitors (e.g., vanadic acid and the like), dipeptidylpeptidase IV inhibitors (e.g., NVP-DPP-278, PT-100, P32/98, LAF-237

and the like), β 3 agonists (e.g., CL-316243, SR-58611-A, UL-TG-307, SB-226552, AJ-9677, BMS-196085, AZ40140 and the like), gluconeogenesis inhibitors (e.g., glycogen phosphorylase inhibitors, glucose-6-phosphatase inhibitors, glucagon antagonists, somatostatin receptor agonists and the like), SGLT (sodium-glucose cotransporter) inhibitors (e.g., T-1095 and the like) and the like.

Examples of the therapeutic agent of diabetic complications include aldose reductase inhibitors (e.g., Tolrestat, Epalrestat, Zenarestat, Zopolrestat, Minalrestat, Fidarestat, SNK-860, CT-112 and the like), neurotrophic factors and increasing drugs thereof (e.g., NGF, NT-3, BDNF; neurotrophin production-secretion promoters described in WO01/14372 (e.g., 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-[3-(2-methylphenoxy)propyl]oxazole and the like) and the like), neuragenesis stimulators (e.g., Y-128 and the like), PKC inhibitors (e.g., LY-333531 and the like), AGE inhibitors (e.g., ALT946, pimagedine, pyratoxanthine, N-phenacylthiazolium bromide (ALT766), EXO-226 and the like), active oxygen scavengers (e.g., thiocctic acid and the like), cerebral vasodilators (e.g., tiapride, mexiletine and the like), and the like.

Examples of the antihyperlipemia agent include statin compounds which are cholesterol synthesis inhibitors (e.g., cerivastatin, pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin, itavastatin and salts thereof (e.g., sodium salt) and the like), squalene synthase inhibitors (e.g., compounds described in WO97/10224, such as N-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzooxazepin-3-yl]acetyl]-piperidine-4-acetic acid and the like) or fibrate compounds having a triglyceride lowering action (e.g., bezafibrate, clofibrate, simfibrate, clinofibrate and

the like), ACAT inhibitors (e.g., Avasimibe, Eflucimibe and the like); anion exchange resins (e.g., colestyramine and the like), probucol, nicotinic acid drugs (e.g., nicomol, niceritrol and the like), éthyl 5 icosapentate, plant sterols (e.g., soysterol, γ -oryzanol and the like) and the like.

Examples of the antihypertensive agent include angiotensin converting enzyme inhibitors (e.g., captopril, enalapril, delapril and the like) or 10 angiotensin II antagonists (e.g., candesartan cilexetil, losartan, eprosartan, valsartan, telmisartan, irbesartan, tasosartan and the like), calcium antagonists (e.g., manidipine, nifedipine, amlodipine, efondipine, nicardipine and the like), potassium channel openers 15 (e.g., levocromakalim, L-27152, AL 0671, NIP-121 and the like), Clonidine and the like.

Examples of the antiobestic agent include central 20 antiobestic agents (e.g., Dexfenfluramine, fenfluramine, phentermine, Sibutramine, amfepramone, dexamphetamine, Mazindol, phenylpropanolamine, clobenzorex and the like), pancreatic lipase inhibitors (e.g., orlistat and the like), β 3 agonists (e.g., CL-316243, SR-58611-A; UL-TG- 25 307, SB-226552, AJ-9677, BMS-196085, AZ40140 and the like), peptide anorexiants (e.g., leptin, CNTF (Ciliary Neurotropic Factor) and the like), cholecystokinin agonists (e.g., sibutramine, FPL-15849 and the like) and the like.

Examples of the diuretic include xanthine derivatives (e.g., sodium salicylate and theobromine, 30 calcium salicylate and theobromine and the like), thiazide preparations (e.g., ethiazide, cyclopenthiazide, trichloromethiazide, hydrochlorothiazide, hydroflumethiazide, benzylhydrochlorothiazide, penflutiazide, polythiazide, methyclothiazide and the like), 35 antialdosterone agents (e.g., spironolactone, triamterene and the like), carbonate dehydrating enzyme

inhibitors (e.g., acetazolamide and the like), chlorobenzenesulfonamide agents (e.g., chlortalidone, mefruside, indapamide and the like), azosemide, isosorbide, etacrynic acid, piretanide, bumetanide, 5 furosemide and the like.

Examples of the chemotherapeutic agent include alkylation agents (e.g., cyclophosphamide, ifosfamide and the like), metabolic antagonists (e.g., methotrexate, 5-fluorouracil and the like), anti-cancer antibiotics (e.g., mitomycin, adriamycin and the like), plant-derived anti-cancer agents (e.g., vincristin, vindesine, taxol and the like), cisplatin, carboplatin, etoposide and the like. Of these, furtulon and neofurtulon which are 5-fluorouracil derivatives and the like are preferable.

Examples of the immunotherapeutic agent include microorganism or bacterial components (e.g., muramyl dipeptide derivative, picibanil and the like), polysaccharides having immunity potentiating activity (e.g., lentinan, sizofiran, krestin and the like), cytokines obtained by genetic engineering techniques (e.g., interferon, interleukin (IL) and the like), colony stimulating factors (e.g., granulocyte stimulating factor, erythropoietin and the like) and the like, with preference given to IL-1, IL-2, IL-12 and the like.

Examples of the antithrombotic agent include heparin (e.g., heparin sodium, heparin calcium, dalteparin sodium and the like), warfarin (e.g., warfarin potassium and the like), anti-thrombin drugs (e.g., aragatrobam and the like), thrombolytic agents (e.g., urokinase, tisokinase, alteplase, nateplase, monteplase, pamiteplase and the like), platelet aggregation inhibitors (e.g., ticlopidine hydrochloride, cilostazol, ethyl icosapentate, beraprost sodium, sarpogrelate hydrochloride and the like) and the like.

Examples of the therapeutic agent of osteoporosis include alfalcacidol, calcitriol, elcaltonin, calcitonin salmon, estriol, ipriflavone, pamidronate disodium, alendronate sodium hydrate, incadronate disodium and the like.

5 Examples of the antidementia agent include tacrine, donepezil, rivastigmine, galantamine and the like.

10 Examples of the agent for improving erectile dysfunction include apomorphine, sildenafil citrate and the like.

15 Examples of the therapeutic agent of incontinencia or pollakiuria include flavoxate hydrochloride, oxybutynin hydrochloride, propiverine hydrochloride and the like.

20 Furthermore, drugs having a cachexia-improving action established in animal models and clinical situations, such as cyclooxygenase inhibitors (e.g., Indometacin and the like) [Cancer Research, vol. 49, 5935-5939, 1989], Progesterone derivatives (e.g., Megesterol acetate) [Journal of Clinical Oncology, vol. 12, 213-225, 1994], glucocorticoid (e.g., dexamethasone and the like), metoclopramide agents, tetrahydrocannabinol agents (*ibid.*), fat metabolism improving agents (e.g., eicosapentaenoic acid and the like) [British Journal of Cancer, vol. 68, 314-318, 1993], growth hormones, IGF-1, or antibodies to a cachexia-induced factor such as TNF- α , LIF, IL-6, Oncostatin M and the like, can be used in combination with the compound of the present invention.

25 The combination drug is preferably an insulin preparation, an insulin sensitizer, an α -glucosidase inhibitor, a biguanide, an insulin secretagogue (preferably a sulfonylurea) or the like.

30 Two or more of the above-mentioned combination drugs can be used in combination in an appropriate ratio. Preferable combinations in the case of using two or

more combination drugs are, for example, as shown in the following.

- 1) an insulin secretagogue (preferably a sulfonylurea) and an α -glucosidase inhibitor;
- 5 2) an insulin secretagogue (preferably a sulfonylurea) and a biguanide;
- 3) an insulin secretagogue (preferably a sulfonylurea), a biguanide and an α -glucosidase inhibitor;
- 4) an insulin sensitizer and an α -glucosidase inhibitor;
- 10 5) an insulin sensitizer and a biguanide;
- 6) an insulin sensitizer, a biguanide and an α -glucosidase inhibitor.

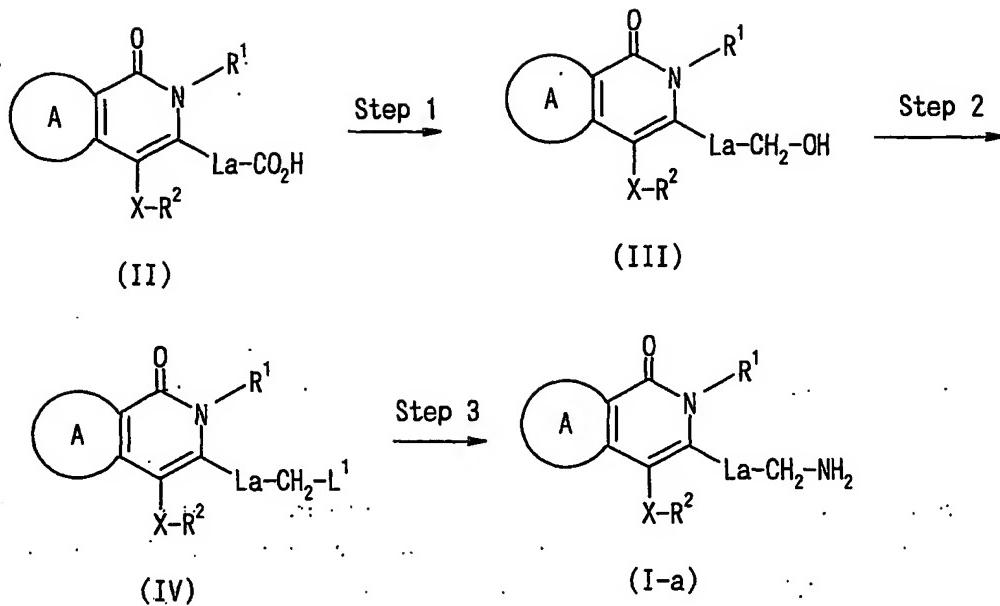
When the compound of the present invention or the pharmaceutical agent of the present invention is used in combination with a combination drug, the amount thereof can be reduced within a safe range in consideration of counteraction of these agents. Particularly, the dose of an insulin sensitizer, an insulin secretagogue (preferably a sulfonylurea) and a biguanide can be reduced as compared with the normal dose. Therefore, an adverse effect which may be caused by these agents can be prevented safely. In addition, the dose of the therapeutic agent of diabetic complications, antihyperlipemia agent and antihypertensive agent can be reduced whereby an adverse effect which may be caused by these agents can be prevented effectively.

Hereinafter the production methods of the compound of the present invention are explained.

The compound of the present invention can be produced according to a method known *per se*, such as a method to be described in detail in the following, or an analogous method thereto.

For example, compound (I-a) of the formula (I) wherein L is alkylene can be produced according to the following Method A or an analogous method thereto.

[Method A]



wherein La is a bond or alkylene, L¹ is a leaving group,
5 and other symbols are as defined above.

The alkylene for La is exemplified by that mentioned as the aforementioned L. When L is alkylene, L is the same as $\text{La}(\text{CH}_2)_n$.

The leaving group for L¹ may be, for example, 10 halogen atom (e.g., chlorine, bromine, iodine and the like), optionally halogenated C₁₋₆ alkylsulfonyloxy (e.g., methanesulfonyloxy, ethanesulfonyloxy, trifluoromethanesulfonyloxy and the like), optionally substituted C₆₋₁₀ arylsulfonyloxy, hydroxy and the like.

15 Examples of the substituent in the "optionally substituted C₆₋₁₀ arylsulfonyloxy" include halogen atom (e.g., chlorine, bromine, iodine and the like), optionally halogenated C₁₋₆ alkyl or C₁₋₆ alkoxy and the like. The number of the substituent(s) is, for example,
20 1 to 3. Specific examples of the "optionally substituted C₆₋₁₀ arylsulfonyloxy" include benzenesulfonyloxy, p-toluenesulfonyloxy, 1-

naphthalenesulfonyloxy, 2-naphthalenesulfonyloxy and the like.

- The "leaving group" is preferably halogen atom (e.g., chlorine, bromine, iodine and the like),
5 methanesulfonyloxy, trifluoromethanesulfonyloxy, p-toluenesulfonyloxy and the like.

(Step 1)

This reaction is carried out by directly reducing with a reducing agent (e.g., borane, lithium aluminum hydride and the like) in a solvent that does not adversely influence the reaction, or converting a carboxyl group to its reactive derivative (e.g., acid halide, mixed acid anhydride, active ester, ester and the like) and reducing with a reducing agent (e.g.,
10 sodium borohydride, sodium lithium borohydride, lithium aluminum hydride, diisobutyl aluminum hydride and the like).
15

The amount of the reducing agent to be used is preferably from about 0.5 to about 10 molar equivalents
20 per compound (II).

The solvent that does not adversely influence the reaction varies depending on the reducing agent.
Examples thereof include aromatic hydrocarbons such as benzene, toluene, xylene and the like; halogenated
25 hydrocarbons such as chloroform, dichloromethane and the like; ethers such as tetrahydrofuran, 1,2-dimethoxyethane, dioxane, diethyl ether and the like; water; alcohols such as methanol, ethanol, isopropanol and the like; and the like. Two or more of these
30 solvents may be used upon mixing at a suitable ratio.

The reaction temperature is generally from about 50°C to about 150°C, preferably about -10°C to about 100°C.

The reaction time is generally from about 0.5 to
35 about 20 hours.

The compound (III) thus obtained can be isolated

and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and
5 the like.

(Step 2)

When L¹ is a halogen atom, this reaction is carried out using a halogenating agent in a solvent that does not adversely influence the reaction.

10 Examples of the halogenating agent include thionyl chloride, phosphorus tribromide and the like.

The amount of the halogenating agent to be used is preferably 1 to about 20 molar equivalents per compound (III).

15 Examples of the solvent that does not adversely influence the reaction include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like, and the like. Two or more of these solvents may be used upon mixing at a suitable ratio. It is also possible to use an excess halogenating agent as a solvent.

The reaction temperature is generally from about 25 20°C to about 150°C, preferably about 0°C to about 100°C.

The reaction time is generally from about 0.1 to about 20 hours.

When L¹ is an optionally halogenated C₁₋₆ alkylsulfonyloxy or an optionally substituted C₆₋₁₀ arylsulfonyloxy, this reaction is carried out using a sulfonylating agent in the presence of a base in a solvent that does not adversely influence the reaction.

30 Examples of the sulfonylating agent include mesyl chloride, tosyl chloride, benzenesulfonyl chloride and
35 the like.

Examples of the base include amines such as

triethylamine, N-methylmorpholine, N,N-dimethylaniline and the like; alkali metal salts such as sodium hydrogencarbonate, sodium carbonate, potassium carbonate and the like; and the like.

5 The amount of the sulfonylating agent and the base to be used is preferably 1 to about 2 molar equivalents per compound (III).

10 Examples of the solvent that does not adversely influence the reaction include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; ethyl acetate and the like.

15 Two or more of these solvents may be used upon mixing at a suitable ratio.

The reaction temperature is generally about -20°C to about 150°C, preferably about 0°C to about 100°C.

The reaction time is generally from about 0.1 to about 20 hours.

20 The thus-obtained compound (IV) can be isolated and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

(Step 3)

This reaction is carried out by reacting compound (IV) and an aminating agent in a solvent that does not adversely influence the reaction, and subjecting the obtained compound to deprotection of an amino group as necessary.

Examples of the aminating agent include ammonia, hexamethylenetetramine, potassium phthalimide, di-t-butyl dicarboxylimide and the like.

35 The amount of the aminating agent to be used is preferably about 1 to about 5 molar equivalents per

compound (IV).

Examples of the solvent that does not adversely influence the reaction include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; alcohols such as methanol, ethanol, isopropanol and the like; ketones such as acetone, 2-butanone and the like; amides such as N,N-dimethylformamide and the like; sulfoxides such as dimethyl sulfoxide and the like; and the like. Two or more of these solvents may be used upon mixing at a suitable ratio.

The reaction temperature is about 0°C to about 200°C, preferably about 20°C to about 120°C.

The reaction time is generally from about 0.5 to about 20 hours.

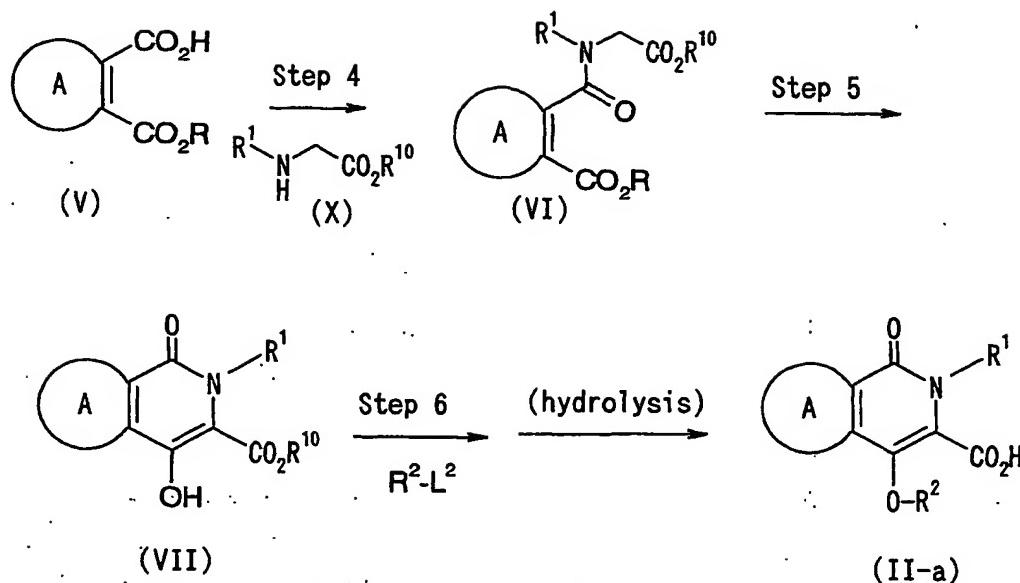
The amino group is deprotected according to a method known *per se*.

The thus-obtained compound (I-a) can be isolated and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

The compound (II) used as a starting material compound in Method A can be produced according to a method known *per se*, for example, the methods detailed in the following or analogous methods thereto.

The compound (II-a) which is a compound of the formula (II) wherein La is a bond and X is -O- can be produced according to the method described in, for example, Journal of Heterocyclic chemistry, vol. 7, 1057 (1970), the following Method B, or analogous methods thereto.

[Method B]



wherein R is a C_{1-6} alkyl group, R^{10} is a hydrogen atom or an optionally substituted hydrocarbon group, L^2 is a leaving group and other symbols are as defined above.

Examples of the C_{1-6} alkyl group for R include methyl, ethyl and the like.

The "optionally substituted hydrocarbon group" for R^{10} is exemplified by that mentioned as the aforementioned R^3 .

The leaving group for L^2 is exemplified by that mentioned as the aforementioned L^1 . The leaving group for L^2 may be a hydroxy group.

15 (Step 4)

This reaction is carried out according to, for example, a method comprising direct condensation of compound (V) and glycine derivative (X) using a condensation agent (e.g., dicyclohexylcarbodiimide and the like), or a method comprising appropriately reacting a reactive derivative of compound (V) and a glycine derivative and the like. Examples of the reactive

derivative include acid anhydride, acid halide (e.g., acid chloride, acid bromide), imidazolide, or mixed acid anhydride (e.g., anhydride with methyl carbonate, ethyl carbonate or isobutyl carbonate and the like) and the like.

When, for example, acid halide is used as a reactive derivative of compound (V), the reaction is carried out in the presence of a base in a solvent that does not adversely influence the reaction.

Examples of the base include amines such as triethylamine, N-methylmorpholine, N,N-dimethylaniline and the like; alkali metal salts such as sodium hydrogencarbonate, sodium carbonate, potassium carbonate and the like; and the like.

Examples of the solvent that does not adversely influence the reaction include halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; ethyl acetate, water and the like. Two or more of these solvents may be used upon mixing at a suitable ratio.

The amount of the glycine derivative (X) to be used is 0.1 to 10 molar equivalents, preferably 1 to 3 molar equivalents, per compound (V).

The reaction temperature is about -30°C to about 100°C.

The reaction time is generally 0.5 to 20 hours.

When a mixed acid anhydride is used as a reactive derivative of compound (V), compound (V) and chlorocarbonate ester (e.g., methyl chlorocarbonate, ethyl chlorocarbonate, isobutyl chlorocarbonate and the like) are reacted in the presence of a base and then reacted with glycine derivative (X).

Examples of the base include amines such as triethylamine, N-methylmorpholine, N,N-dimethylaniline

and the like; alkali metal salts such as sodium hydrogencarbonate, sodium carbonate, potassium carbonate and the like; and the like.

The amount of the glycine derivative (X) to be used
5 is generally 0.1 to 10 molar equivalents, preferably 0.3 to 3 molar equivalents, per compound (V).

The reaction temperature is generally from about -30°C to about 100°C.

The reaction time is generally from 0.5 to 20 hours.

10 The thus-obtained compound (VI) can be isolated and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and
15 the like.

The compound (V) and glycine derivative (X) used as a starting material compound in step 4 can be produced according to a method known *per se*.

(Step 5)

20 This reaction is carried out according to a conventional method in the presence of a base in a solvent that does not adversely influence the reaction.

Examples of the base include metalhydrides such as sodium hydride, potassium hydride and the like; alkali metal alkoxides such as sodium methoxide, sodium ethoxide, potassium t-butoxide and the like; alkali metal salts such as potassium hydroxide, sodium hydroxide, sodium hydrogencarbonate, potassium carbonate and the like; amines such as pyridine, triethylamine,
25 N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undeca-7-ene and the like.

The amount of the base to be used is preferably about 0.1 to about 2 molar equivalents per compound (VI).

30 Examples of the solvent that does not adversely influence the reaction include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers

such as tetrahydrofuran, dioxane, diethyl ether and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; water; alcohols such as methanol, ethanol, isopropanol and the like; ketones such as acetone, 2-butanone and the like; amides such as N,N-dimethylformamide and the like; sulfoxides such as dimethyl sulfoxide and the like; and the like. Two or more of these solvents may be used upon mixing at a suitable ratio.

The reaction temperature is about -10°C to about 150°C, preferably about 0°C to about 110°C.

The reaction time is generally from about 0.5 to about 20 hours.

The thus-obtained compound (VII) can be isolated and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

20 (Step 6)

When L² is a hydroxy group, this reaction is carried out by a method known *per se*, such as a method described in Synthesis, page 1 (1981), or an analogous method thereto.

This reaction is generally carried out in the presence of an organic phosphorus compound and electrophil in a solvent that does not adversely influence the reaction.

Examples of the organic phosphorus compound include triphenylphosphine, tributylphosphine and the like.

Examples of the electrophil include diethyl azodicarboxylate, diisopropyl azodicarboxylate, azodicarbonyldipiperazine and the like.

The amount of the organic phosphorus compound and electrophil to be used is preferably about 1 to about 5 molar equivalents per compound (VII).

Examples of the solvent that does not adversely influence the reaction include ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; halogenated hydrocarbons such as chloroform, 5 dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; amides such as N,N-dimethylformamide and the like; sulfoxides such as dimethyl sulfoxide and the like; and the like. Two or more of these solvents may be used upon mixing at a 10 suitable ratio.

The reaction temperature is about -50°C to about 150°C, preferably about -10°C to about 100°C.

The reaction time is generally from about 0.5 to about 20 hours.

15 When L² is a halogen atom, an optionally halogenated C₁₋₆ alkylsulfonyloxy or an optionally substituted C₆₋₁₀ arylsulfonyloxy, this reaction is carried out according to a conventional method in the presence of a base in a solvent that does not adversely 20 influence the reaction.

Examples of the base include alkali metal salts such as potassium hydroxide, sodium hydroxide, sodium hydrogen carbonate; potassium carbonate and the like; amines such as pyridine, triethylamine, N,N- 25 dimethylaniline, 1,8-diazabicyclo[5.4.0]undeca-7-ene and the like; metalhydrides such as potassium hydride, sodium hydride and the like; alkali metal alkoxides such as sodium methoxide, sodium ethoxide, potassium t-butoxide and the like; and the like.

30 The amount of the base to be used is preferably about 1 to about 5 molar equivalents per compound (VII).

Examples of the solvent that does not adversely influence the reaction include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers 35 such as tetrahydrofuran, dioxane, diethyl ether and the like; ketones such as acetone, 2-butanone and the like;

halogenated hydrocarbons such as chloroform,
dichloromethane and the like; amides such as N,N-
dimethylformamide and the like; sulfoxides such as
dimethyl sulfoxide and the like; and the like. Two or
5 more of these solvents may be used upon mixing at a
suitable ratio.

The reaction temperature is generally about -50°C to about 150°C, preferably about -10°C to about 100°C.

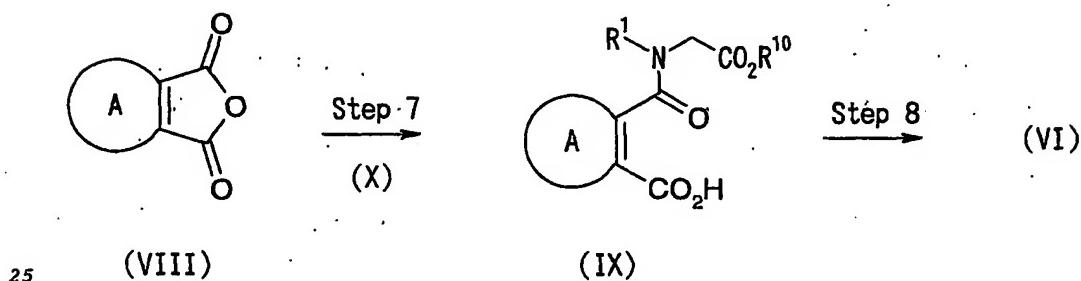
The reaction time is generally from about 0.5 to
10 about 20 hours.

The compound obtained from the aforementioned step 6 is hydrolyzed, where necessary, by a method known *per se* to give compound (II-a).

The thus-obtained compound (II-a) can be isolated
15 and purified by a known separation and purification
means, such as concentration, concentration under
reduced pressure, solvent extraction, crystallization,
recrystallization, phase transfer, chromatography and
the like.

20 The compound (VI) to be used in the aforementioned Method B can be also produced according to the following Method C.

[Method C]



wherein the symbols are as defined above.

(Step 7)

This reaction is carried out according to a conventional method in a solvent that does not adversely

influence the reaction.

Examples of the solvent that does not adversely influence the reaction include halogenated hydrocarbons such as chloroform, dichloromethane and the like;

5 aromatic hydrocarbons such as benzene, toluene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; ethyl acetate and the like. Two or more of these solvents may be used upon mixing at a suitable ratio.

10 The amount of the glycine derivative (X) to be used is about 1 to about 10 molar equivalents, preferably 1 to 3 molar equivalents per compound (VIII).

The reaction temperature is generally from -30°C to 100°C.

15 The reaction time is generally from 0.5 to 20 hours.

The thus-obtained compound (IX) can be isolated and purified by a known separation and purification means, such as concentration, concentration under reduced

20 pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

The compound (VIII) used as a starting material compound in Step 7 can be produced according to a method

25 known *per se*.

(Step 8)

This reaction is carried out according to a conventional method in the presence of a base and a C₁-₆ alkyl halide in a solvent that does not adversely influence the reaction.

Examples of the base include alkali metal salts such as potassium hydroxide, sodium hydroxide, sodium hydrogencarbonate, potassium carbonate and the like; amines such as pyridine, triethylamine, N,N-

35 dimethylaniline, 1,8-diazabicyclo[5.4.0]undeca-7-ene and the like.

The amount of the base to be used is preferably about 1 to about 2 molar equivalents per compound (IX).

Examples of the C₁₋₆ alkyl halide include iodomethane, iodoethane and the like.

5 The amount of the C₁₋₆ alkyl halide to be used is preferably about 1 to about 2 molar equivalents per compound (IX).

Examples of the solvent that does not adversely influence the reaction include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; ketones such as acetone, 2-butanone and the like; amides such as N,N-dimethylformamide and the like; sulfoxides such as dimethyl sulfoxide and the like; and the like. Two or more of these solvents may be used upon mixing at a suitable ratio.

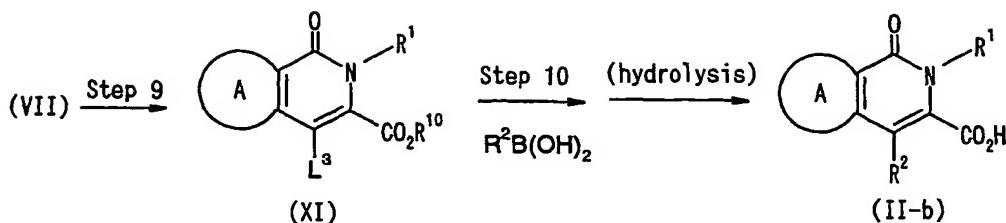
The reaction temperature is generally from about 20 10°C to about 150°C, preferably 0°C to 110°C.

The reaction time is generally from about 0.5 to about 20 hours.

The thus-obtained compound (VI) can be isolated and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

The compound (II-b) which is a compound of the formula (II) wherein La is a bond and X is a bond can be produced by a method described in, for example, JP-A-7-76573, JP-A-2000-72751 or JP-A-2000-72675, the following Method D or analogous methods thereto.

[Method D]



wherein L^3 is a leaving group, and other symbols are as defined above.

- 5 The leaving group for L^3 is exemplified by that mentioned as the aforementioned L^1 .

(Step 9).

When, for example, L^3 is an optionally halogenated C_{1-6} alkylsulfonyloxy or an optionally substituted C_{6-10} 10 arylsulfonyloxy, this reaction is carried out according to a conventional method in the presence of a base and a sulfonylating agent in a solvent that does not adversely influence the reaction.

Examples of the base include metalhydrides such as 15 sodium hydride, potassium hydride and the like; alkali metal alkoxides such as sodium methoxide, sodium ethoxide, potassium t-butoxide and the like; alkali metal salts such as potassium hydroxide, sodium hydroxide, sodium hydrogencarbonate, potassium carbonate and the like; amines such as pyridine, triethylamine, 20 N,N -dimethylaniline, 1,8-diazabicyclo[5.4.0]undeca-7-ene and the like.

The amount of the base to be used is preferably about 1 to about 5 molar equivalents per compound (VII).

25 Examples of the sulfonylating agent include N -phenyltrifluoromethanesulfonimide, anhydrous trifluoromethanesulfonic acid and the like.

The amount of the sulfonylating agent to be used is preferably about 1 to about 5 molar equivalents per 30 compound (VII).

Examples of the solvent that does not adversely

influence the reaction include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; halogenated hydrocarbons such as chloroform, 5 dichloromethane and the like; and the like. Two or more of these solvents may be used upon mixing at a suitable ratio.

The reaction temperature is generally from about -50°C to about 150°C, preferably about -10°C to about 20°C.

10 The reaction time is generally from about 0.5 to about 20 hours.

The thus-obtained compound (XI) can be isolated and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

(Step 10)

This reaction is carried out according to a conventional method in the presence of a base and a metal catalyst in a solvent that does not adversely influence the reaction under an inert gas atmosphere.

Examples of the base include metalhydrides such as sodium hydride, potassium hydride and the like; alkali metal alkoxides such as sodium methoxide, sodium ethoxide, potassium t-butoxide and the like; alkali metal salts such as potassium hydroxide, sodium hydroxide, sodium hydrogencarbonate, sodium carbonate, potassium carbonate and the like; amines such as 30 pyridine, triethylamine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undeca-7-ene and the like. Of these, alkali metal salts such as sodium hydrogencarbonate, sodium carbonate, potassium carbonate and the like are preferable.

35 The amount of the base to be used is preferably about 1 to about 5 molar equivalents per compound (XI).

Examples of the metal catalyst include palladium complex such as tetrakis(triphenylphosphine)palladium(0) and the like.

- The amount of use of the metal catalyst is
5 preferably about 0.01 to about 0.5 molar equivalents per compound (XI).

Examples of the solvent that does not adversely influence the reaction include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers
10 such as tetrahydrofuran, dioxane, diethyl ether and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; water; alcohols such as methanol, ethanol, isopropanol and the like; ketones such as acetone, 2-butanone and the like; amides such as
15 N,N-dimethylformamide and the like; sulfoxides such as dimethyl sulfoxide and the like; and the like. Two or more of these solvents may be used upon mixing at a suitable ratio.

Examples of the inert gas include argon, nitrogen
20 and the like.

The reaction temperature is generally from about -10°C to about 150°C, preferably about 0°C to about 100°C.

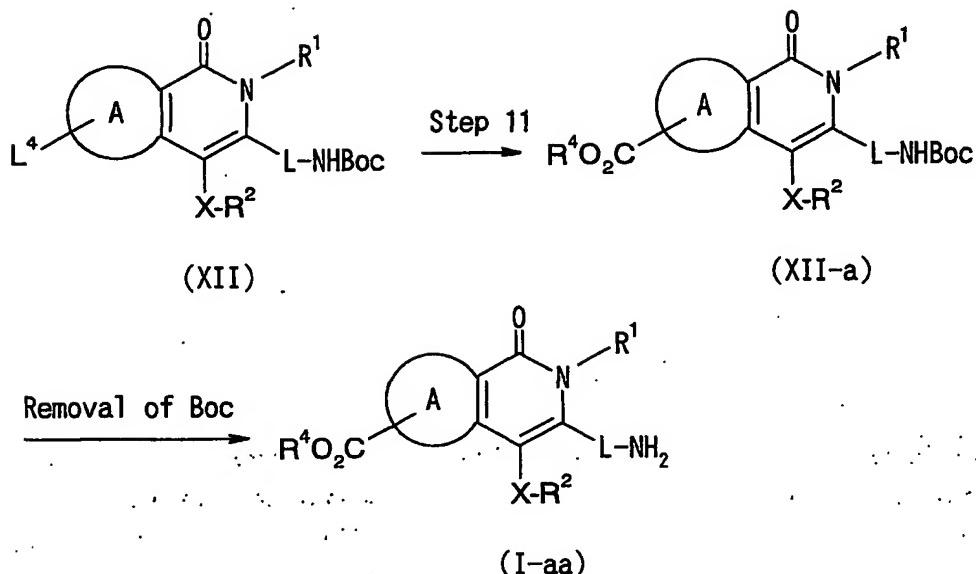
The reaction time is generally from about 0.5 to about 20 hours.

25 The compound obtained from Step 10 is hydrolyzed according to a method known *per se* to give compound (II-b).

The compound (II-b) can be isolated and purified by a known separation and purification means, such as
30 concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

The compound (I-aa) wherein ring A has a group of the formula: -CO-OR⁴ (R⁴ is as defined above) as a
35 substituent can be also produced by the following Method E.

[Method E]



5 wherein L⁴ is a leaving group, Boc is a t-butoxycarbonyl group and other symbols are as defined above.

The leaving group for L⁴ is exemplified by that mentioned as the aforementioned L¹.

(Step 11)

10 This reaction is carried out in the presence of carbon monoxide, a metal catalyst, a reaction reagent and an alcohol in a solvent that does not adversely influence the reaction.

The metal catalyst is, for example, a palladium catalyst (e.g., palladium acetate and the like).

The amount of the metal catalyst to be used is preferably about 0.01 to about 1 molar equivalent per compound (XII).

The reaction reagent is, for example, an organic
20 phosphorus compound (e.g., 1,3-
bis(diphenylphosphino)propane and the like), a base
(e.g., amines such as pyridine, triethylamine, N,N-

dimethylaniline etc., and the like), and the like.

The amount of the reaction reagent to be used is preferably about 1 to about 5 molar equivalents per compound (XII).

5 As the alcohol, an excess amount of ethanol or methanol is generally used.

Examples of the solvent that does not adversely influence the reaction include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers

10 such as tetrahydrofuran, dioxane, diethyl ether and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; amides such as N,N-dimethylformamide and the like; sulfoxides such as dimethyl sulfoxide and the like; and the like. Two or
15 more of these solvents may be used upon mixing at a suitable ratio.

The reaction temperature is generally from about 0°C to about 150°C, preferably about 50°C to about 100°C.

20 The reaction time is generally from about 0.5 to about 20 hours.

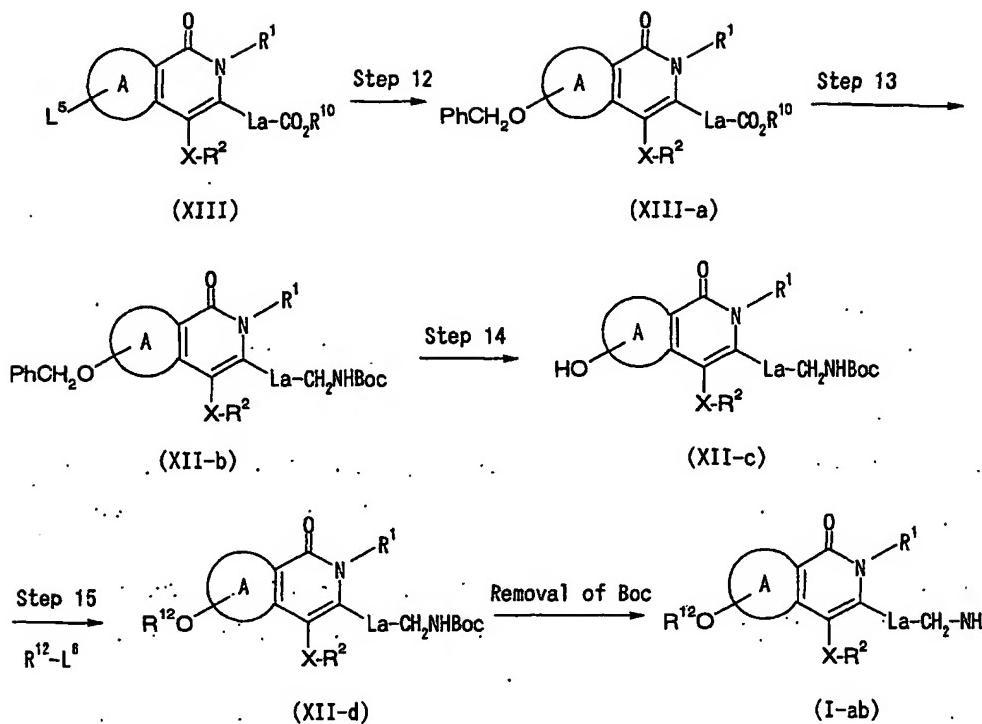
From compound (XII-a) obtained from Step 11, Boc group is removed by a method known per se to give compound (I-aa).

25 The thus-obtained compound (I-aa) can be isolated and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

30 The compound (XII) used as a starting material compound in Method E can be produced according to, for example, the aforementioned Method A or an analogous method thereto.

35 The compound (I-ab) wherein ring A has an optionally substituted hydroxy group as a substituent can be also produced by the following Method F.

[Method F]



5 wherein L⁵ and L⁶ are leaving group, R¹² is an optionally substituted hydrocarbon group and other symbols are as defined above.

The leaving group for L⁵ and L⁶ are exemplified by that mentioned as the aforementioned L¹.

10 Examples of the "optionally substituted hydrocarbon group" for R¹² include each optionally substituted "alkyl group having 1 to 10 carbon atom(s)", "alkenyl group having 2 to 10 carbon atoms", "alkynyl group having 2 to 10 carbon atoms", "cycloalkyl group having 3 to 10
15 carbon atoms", "cycloalkenyl group having 3 to 10 carbon atoms", "aryl group having 6 to 14 carbon atoms" and "aralkyl having 7 to 13 carbon atoms" mentioned in the "optionally substituted hydroxy group" as the substituent in ring A.

(Step 12)

This reaction is carried out using benzyl alcohol in the presence of a base in a solvent that does not adversely influence the reaction.

- 5 Examples of the base include alkali metal salts such as potassium hydroxide, sodium hydroxide, sodium hydrogencarbonate, potassium carbonate and the like; amines such as pyridine, triethylamine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undeca-7-ene and
10 the like; metalhydrides such as potassium hydride, sodium hydride and the like; alkali metal alkoxides such as sodium methoxide, sodium ethoxide, potassium t.-butoxide and the like; and the like.

The amount of the base to be used is preferably about 1 to about 5 molar equivalents per compound (XIII).

The amount of benzyl alcohol to be used is preferably about 1 to about 3 molar equivalents per compound (XIII).

- Examples of the solvent that does not adversely influence the reaction include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; amides such as N,N-dimethylformamide and the like; sulfoxides such as dimethyl sulfoxide and the like; and the like. Two or more of these solvents may be used upon mixing at a suitable ratio.

The reaction temperature is generally from about 30 0°C to about 150°C, preferably about 50°C to about 100°C.

The reaction time is generally from about 0.5 to about 20 hours.

- The thus-obtained compound (XIII-a) can be isolated and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization,

recrystallization, phase transfer, chromatography and the like.

(Step 13)

This reaction is carried out by introducing a Boc group according to a method known *per se* after reaction in the same manner as in the aforementioned Steps 1 to 3.

The thus-obtained compound (XII-b) can be isolated and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

(Step 14)

This reaction is carried out according to a *per se* known hydrogenation under a hydrogen atmosphere or in the presence of a hydrogen source such as formic acid and the like and a metal catalyst in a solvent that does not adversely influence the reaction.

Examples of the metal catalyst include a transition metal catalyst such as palladium-carbon, palladium black, platinum oxide, Raney-nickel, Wilkinson's catalyst etc., and the like.

The amount of the metal catalyst to be used is preferably about 0.01 to about 10 molar equivalents per compound (XII-b).

Examples of the solvent that does not adversely influence the reaction include lower organic acids such as acetic acid and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; amides such as N,N-dimethylformamide and the like; alcohols such as methanol, ethanol, isopropanol and the like; and the like. Two or more of these solvents may be used upon mixing at a suitable ratio.

The reaction temperature is generally from about 0°C to about 150°C, preferably about 0°C to about 100°C.

The reaction time is generally from about 0.5 to

about 20 hours.

The thus-obtained compound (XII-c) can be isolated and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

(Step 15)

This Step is carried out by the reaction in the same manner as in the aforementioned Step 8.

The thus-obtained compound (XII-d) can be isolated and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

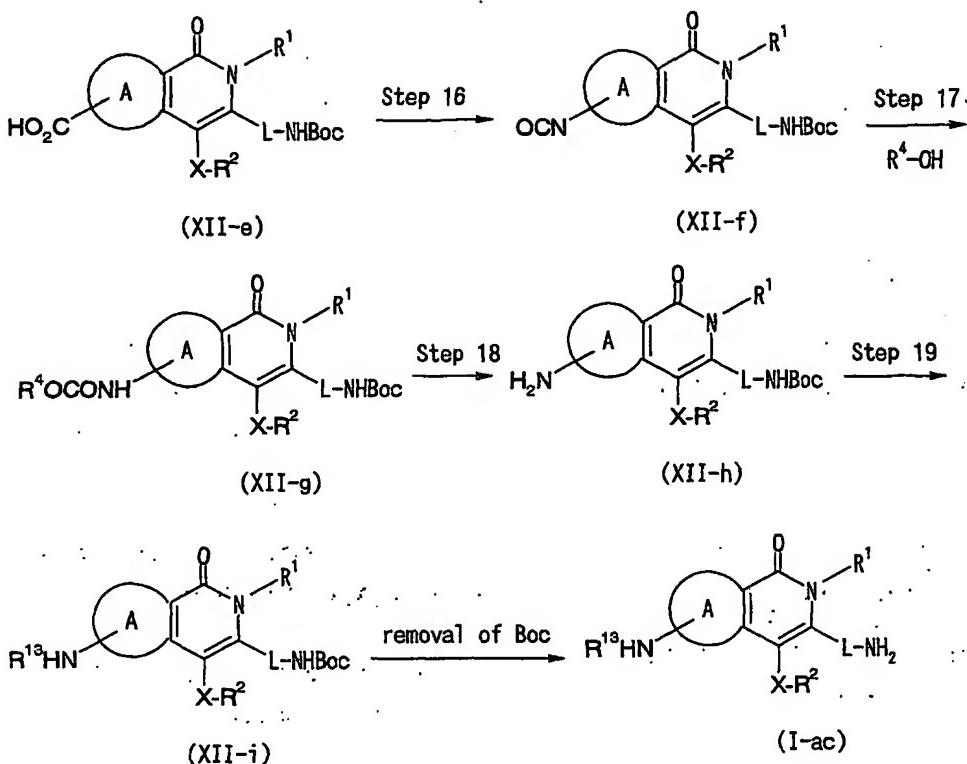
The compound (I-ab) can be produced by removing a Boc group from compound (XII-d) according to a method known *per se*.

The compound (I-ab) can be isolated and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

The compound (XIII) used as a starting material compound in Method F can be produced according to, for example, the aforementioned Method A or an analogous method thereto.

The compound (I-ac) wherein ring A has an optionally substituted amino group as a substituent can be also produced according to the following Method G.

[Method G]



wherein R^{13} is a hydrocarbon group or an acyl group and other symbols are as defined above.

- 5 Examples of the "hydrocarbon group" for R^{13} include "alkyl group having 1 to 10 carbon atom(s)", "alkenyl group having 2 to 10 carbon atoms", "cycloalkyl group having 3 to 10 carbon atoms", "cycloalkenyl group having 3 to 10 carbon atoms" and "aryl group having 6 to 14 carbon atoms" mentioned in the "optionally substituted amino group" as the substituent in ring A. Examples of the acyl group for R^{13} is exemplified by that mentioned as the substituent in ring A.
- 10

(Step 16)

- 15 In this Step, compound (XII-e) and diphenylphosphoryl azide are reacted in the presence of a base in a solvent that does not adversely influence the reaction to give an acyl azide compound, which is

subjected to Curtius rearrangement reaction to give isocyanic acid derivative (XII-f).

The amount of the diphenylphosphoryl azide to be used is 1 to 10 molar equivalent(s), preferably 1.5 to 3
5 molar equivalents, per compound (XII-e).

Examples of the base include amines such as triethylamine, 4-dimethylaminopyridine, triethylenediamine, tetramethylethylenediamine and the like.

10 The amount of the base to be used is preferably about 1 to about 5 molar equivalents per compound (XII-e).

Examples of the solvent that does not adversely influence the reaction include ethers such as diethyl
15 ether, tetrahydrofuran, dioxane and the like; halogenated hydrocarbons such as dichloromethane, dichloroethane, chloroform and the like; dimethylformamide and the like. Two or more of these solvents may be used upon mixing at a suitable ratio.

20 The reaction temperature is -20°C to 50°C, preferably 0°C to 20°C.

The reaction time is from 0.5 to 5 hours, preferably from 1 to 2 hours.

25 The Curtius rearrangement reaction is carried out according to a method known *per se* in a solvent that does not adversely influence the reaction.

Examples of the solvent that does not adversely influence the reaction include hydrocarbons such as benzene, toluene, xylene and the like; ethers such as
30 diethyl ether, tetrahydrofuran, dioxane and the like; halogenated hydrocarbons such as dichloromethane, dichloroethane, chloroform and the like; amides such as dimethylformamide and the like; and the like. Two or more of these solvents may be used upon mixing at a
35 suitable ratio.

The reaction temperature is generally from 50°C to

200°C, preferably 80°C to 150°C.

The reaction time is generally from 0.5 to 12 hours, preferably from 1 to 3 hours.

The thus-obtained compound (XII-f) can be isolated
5 and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

10 (Step 17)

This reaction is carried out in a solvent that does not adversely influence the reaction.

The amount of a compound of the formula: R⁴-OH (wherein the symbols are as defined above) to be used is
15 preferably about 1 to about 5 molar equivalents per compound (XII-f).

Examples of the solvent that does not adversely influence the reaction include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; amides such as N,N-dimethylformamide and the like; sulfoxides such as dimethyl sulfoxide and the like; and the like. Two or 25 more of these solvents may be used upon mixing at a suitable ratio.

The reaction temperature is generally from about 0°C to about 150°C, preferably about 50°C to about 100°C.

The reaction time is generally from about 0.5 to 30 about 20 hours.

This reaction may be carried out in the presence of a catalytic amount of N,N-dimethylaminopyridine and the like.

The thus-obtained compound (XII-g) can be isolated
35 and purified by a known separation and purification means, such as concentration, concentration under.

reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

By using a compound of the formula: $\text{HNR}^{4a}\text{R}^{5a}$

5 (wherein the symbols are as defined above) instead of a compound of the above-mentioned formula: $\text{R}^4\text{-OH}$ (wherein the symbols are as defined above), a compound (XII-g) wherein the substituent: $\text{R}^4\text{OCONH-}$ is replaced by $\text{R}^{4a}\text{R}^{5a}\text{NCONH-}$ can be produced.

10 (Step 18)

This reaction is carried out by deprotection (e.g., catalytic reduction, piperidine treatment and the like) generally employed in peptide chemistry and the like.

The thus-obtained compound (XII-h) can be isolated 15 and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

20 (Step 19)

This reaction is carried out according to a conventional method using an alkylation agent, an acylation agent and the like in the presence of a condensation agent or a base in a solvent that does not 25 adversely influence the reaction.

The alkylation agent is exemplified by alkyl halides, alkylsulfonates and the like.

The amount of the alkylation agent to be used is preferably about 1 to about 5 molar equivalents per 30 compound (XII-h).

The acylation agent is exemplified by carboxylic acid, sulfonic acid, phosphoric acid, carbonic acid or reactive derivatives thereof (e.g., acid halide, acid anhydride, mixed acid anhydride, active ester and the 35 like), isocyanide, isothiocyanide and the like.

The amount of the acylating agent to be used is

preferably about 1 to about 5 molar equivalents per compound (XII-h).

The condensation agent is exemplified by dicyclohexylcarbodiimide, diethyl cyanophosphate, 1-
5 ethyl-3-(3-dimethylaminopropyl)carbodiimide and the like.

The amount of the condensation agent to be used is preferably about 1 to about 5 molar equivalents per compound (XII-h).

Examples of the base include alkali metal salts
10 such as potassium hydroxide, sodium hydroxide, sodium hydrogencarbonate, potassium carbonate and the like; amines such as pyridine, triethylamine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undeca-7-ene and the like; metalhydrides such as potassium hydride,
15 sodium hydride and the like; alkali metal alkoxides such as sodium methoxide, sodium ethoxide, potassium t.-butoxide and the like; and the like.

The amount of the base to be used is preferably about 1 to about 5 molar equivalents per compound (XII-h).

Examples of the solvent that does not adversely influence the reaction include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; ketones such as acetone, 2-butanone and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; amides such as N,N-dimethylformamide and the like; sulfoxides such as dimethyl sulfoxide and the like; and the like. Two or 30 more of these solvents may be used upon mixing at a suitable ratio.

The reaction temperature is generally from about -50°C to about 150°C, preferably about -10°C to about 100°C.

35 The reaction time is generally from about 0.5 to about 20 hours.

The thus-obtained compound (XII-i) can be isolated and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

By removing a Boc group from the thus-obtained compound (XII-i) according to a method known *per se*, compound (I-ac) can be produced.

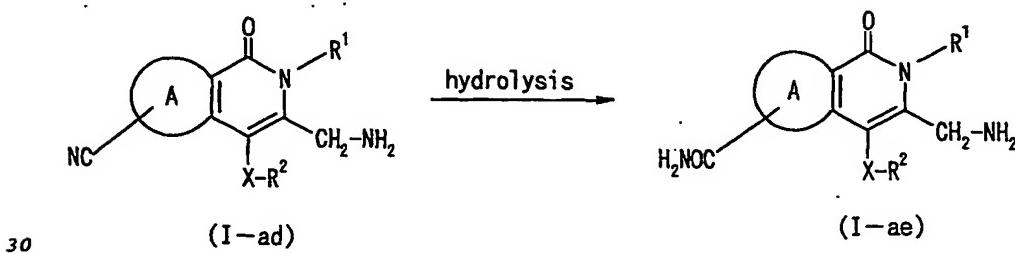
10 The compound (I-ac) can be isolated and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

15 Furthermore, by removing a Boc group from the aforementioned compound (XII-g) and compound (XII-h) according to a method known *per se*, a compound (I-ac) wherein the substituent: $R^{13}HN^-$ is respectively substituted by R^4OCONH^- or amino can be produced.

20 The compound (XII-e) used as a starting material in Method G can be produced according to, for example, the aforementioned Method A, Method E or analogous methods thereto.

25 The compound (I-ae) which is a compound of the formula (I) wherein ring A has a carbamoyl group as a substituent and L is methylene can be also produced by, for example, the following Method H.

[Method H]



wherein the symbols are as defined above.

The hydrolysis can be generally carried out in the presence of an acid or a base.

5 Examples of the acid include mineral acids (e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid and the like), carboxylic acids (e.g., formic acid, acetic acid, propionic acid and the like), and the like. Of these, hydrochloric acid, sulfuric
10 acid and the like are preferable.

Examples of the base include alkali metal salts such as lithium hydroxide, potassium hydroxide, sodium hydroxide, potassium carbonate, sodium carbonate, potassium hydrogencarbonate, sodium hydrogencarbonate
15 and the like; alkaline earth metal salts such as calcium hydroxide, barium hydroxide and the like; amines such as trimethylamine, triethylamine, ethyldiisopropylamine, N-methylmorpholine and the like; and the like. Of these, potassium hydroxide, sodium hydroxide and the like are
20 preferable.

The amount of the acid or base to be used is, for example, 0.01 to 100 molar equivalents, preferably 0.1 to 50 molar equivalents per compound (I-ad).

Hydrolysis is generally conducted in a solvent that
25 does not adversely influence the reaction. Examples of the solvent include alcohols such as methanol, ethanol, propanol, 2-propanol, butanol, isobutanol, tert-butanol and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; aliphatic hydrocarbons
30 such as hexane, heptane and the like; ethers such as diethyl ether, diisopropyl ether, tert-butylmethyl ether, tetrahydrofuran, dioxane, dimethoxyethane and the like; amides such as dimethylformamide, dimethylacetamide and the like; sulfoxides such as dimethyl sulfoxide and the
35 like; water and the like. Two or more of these solvents may be used upon mixing at a suitable ratio.

The reaction temperature is generally from 0°C to 150°C, preferably 10°C to 100°C.

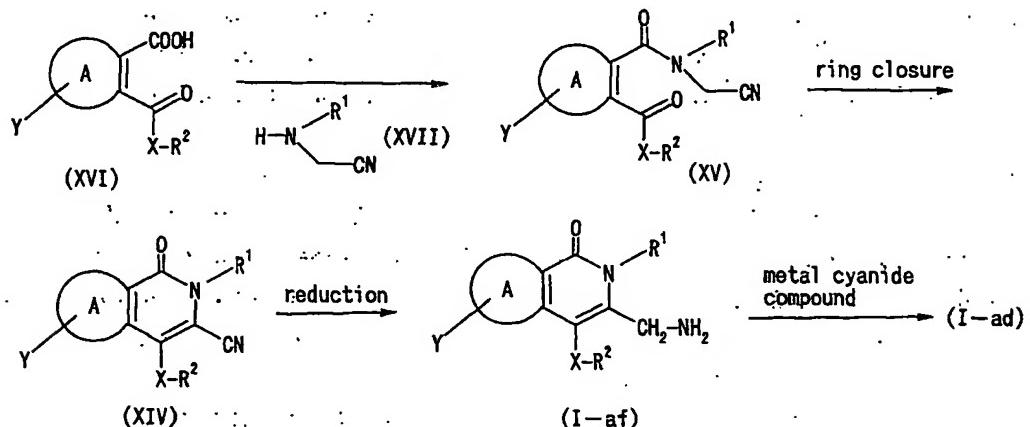
The reaction time is generally from 0.1 to about 100 hours, preferably from 0.1 to 10 hours.

5 The thus-obtained compound (I-ae) can be isolated and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and
10 the like.

The compound (I-ad) used as a starting material compound in Method H can be produced according to, for example, the following Method I.

[Method I]

15



wherein the symbols are as defined above..

In this method, compound (XVI) and compound (XVII)
20 are reacted to give compound (XV).

This reaction is carried out according to a per se known amidation reaction. This method may be, for example, a method comprising direct condensation of compound (XVI) and compound (XVII) using a condensation agent, a method comprising reacting a reactive derivative of compound (XVI) and compound (XVII), and
25

the like.

Examples of the condensation agent include carbodiimide condensation reagents such as dicyclohexylcarbodiimide, diisopropylcarbodiimide, 1-
5 ethyl-3-(3-dimethylaminopropyl)carbodiimide and its hydrochloride, and the like; phosphoric acid condensation reagents such as diethyl cyanophosphate, diphenylphosphoryl azide and the like; carbonyldiimidazole, 2-chloro-1,3-dimethylimidazolium
10 tetrafluoroborate and the like.

Examples of the solvent to be used for a reaction using a condensation agent include amides such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone and the like; sulfoxides such as
15 dimethyl sulfoxide and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether, dimethoxyethane and the like; esters such
20 as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile, propionitrile and the like; water and the like. Two or more of these solvents may be used upon mixing at a suitable ratio.

The amount of the compound (XVII) to be used is
25 generally 1 to 10 molar equivalents, preferably 1 to 3 molar equivalents, per compound (XVI).

The amount of the condensation agent to be used is generally 0.1 to 10 molar equivalents, preferably 0.3 to 3 molar equivalents, per compound (XVI).

30 When a carbodiimide condensation reagent is used as a condensation agent, the reaction efficiency can be increased by the use of a suitable condensation promoter (e.g., 1-hydroxy-7-azabenzotriazole, 1-hydroxybenzotriazole, N-hydroxysuccinimide, N-
35 hydroxyphthalimide and the like) as necessary. When a phosphoric condensation reagent is used as a

condensation agent, the reaction efficiency can be increased by the use of an organic amine base such as triethylamine and the like.

The amount of the above-mentioned condensation promoter and organic amine base to be used is generally 5 0.1 to 10 molar equivalents, preferably 0.3 to 3 molar equivalents, per compound (XVI).

The reaction temperature is generally from -30°C to 120°C, preferably -10°C to 100°C.

10 The reaction time is generally from 0.5 to 60 hours.

The reactive derivative of compound (XVI) may be, for example, acid anhydride, acid halide (acid chloride, acid bromide), imidazolide, mixed acid anhydride (e.g., anhydride with methylcarbonate, ethylcarbonate or

15 isobutylcarbonate and the like) and the like.

When, for example, an acid anhydride or an acid halide is used, the reaction is generally carried out in the presence of a base in a solvent that does not adversely influence the reaction.

20 Examples of the base include amines such as triethylamine, pyridine, N-methylmorpholine, N,N-dimethylaniline, 4-dimethylaminopyridine and the like; alkali metal salts such as lithium hydroxide, sodium hydroxide, potassium hydroxide, sodium hydrogencarbonate, 25 sodium carbonate, potassium carbonate and the like; and the like.

Examples of the solvent that does not adversely influence the reaction include amides such as N,N-dimethylformamide, N,N-dimethylacetamide, N-30 methylpyrrolidone and the like; sulfoxides such as dimethyl sulfoxide and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene and the like; ethers such as tetrahydrofuran, dioxane, 35 diethyl ether, dimethoxyethane and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles

such as acetonitrile, propionitrile and the like; water and the like. Two or more of these solvents may be used upon mixing at a suitable ratio.

When the above-mentioned amides are used as the solvent that does not adversely influence the reaction, the reaction may be carried out in the absence of a base.

The amount of the compound (XVII) to be used is generally 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents, per compound (XVI).

The amount of the base to be used is generally 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents per compound (XVI).

The reaction temperature is generally from -30°C to 100°C, preferably -10°C to 100°C.

The reaction time is generally from 0.5 to 30 hours. When a mixed acid anhydride is used, compound (XVI) and chlorocarbonate (e.g., methyl chlorocarbonate, ethyl chlorocarbonate, isobutyl chlorocarbonate and the like) are reacted in the presence of a base, and the obtained compound is reacted with compound (XVII).

Examples of the base include amines such as triethylamine, aniline, N-methylmorpholine, N,N-dimethylaniline, 4-dimethylaminopyridine and the like; alkali metal salts such as sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium hydrogencarbonate, sodium carbonate, potassium carbonate and the like; and the like.

The amount of the compound (XVII) to be used is generally 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents, per compound (XVI).

The amount of the base to be used is generally 1 to 10 molar equivalents, preferably 1 to 3 molar equivalents per compound (XVI).

The reaction temperature is generally from -30°C to 120°C, preferably -10°C to 100°C.

The reaction time is generally from 0.5 to 20 hours.

The thus-obtained compound (XV) can be isolated and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, 5 recrystallization, phase transfer, chromatography and the like. It is also possible to subject a reaction mixture containing compound (XV) to the next reaction without isolating compound (XV).

The compound (XIV) is produced by subjecting the 10 compound (XV) to a ring closure reaction:

The ring closure reaction is generally carried out in the presence of a base in a solvent that does not adversely influence the reaction.

Examples of the base include amines such as 15 triethylamine; pyridine, N-methylmorpholine, N,N-dimethylaniline, 4-dimethylaminopyridine, 1,5-diazabicyclo[4.3.0]-5-nonene (DBN), 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) and the like; alkali metal salts such as lithium hydroxide, sodium 20 hydroxide, potassium hydroxide, sodium hydrogencarbonate, sodium carbonate, potassium carbonate and the like; and the like.

Examples of the solvent that does not adversely influence the reaction include amides such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone and the like; sulfoxides such as dimethyl sulfoxide and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene and 30 the like; ethers such as tetrahydrofuran, dioxane, diethyl ether, dimethoxyethane and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile, propionitrile and the like; water and the like. Two or more of these solvents may be used 35 upon mixing at a suitable ratio.

The amount of the base to be used is generally 0.01

to 10 molar equivalents, preferably 0.1 to 3 molar equivalents per compound (XV).

The reaction temperature is generally from -30°C to 120°C, preferably -10°C to 100°C.

5 The reaction time is generally from 0.5 to 40 hours.

The thus-obtained compound (XIV) can be isolated and purified by known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, 10 recrystallization, phase transfer, chromatography and the like. It is also possible to subject a reaction mixture containing compound (XIV) to the next reaction without isolating compound (XIV).

The compound (I-af) is produced by reducing 15 compound (XIV).

The reduction is performed according to a conventional method in the presence of a reducing agent in a solvent that does not adversely influence the reaction.

20 Examples of the reducing agent include metal hydrogen compounds such as bis(2-methoxyethoxy)aluminum sodium hydride, diisobutyl aluminum hydride and the like; metal hydrogen complex compounds such as sodium borohydride, sodium cyanide borohydride, aluminum 25 lithium hydride, aluminum sodium hydride and the like; and the like.

The amount of the reducing agent to be used is generally 0.1 to 20 molar equivalents per compound (XIV).

Examples of the solvent that does not adversely 30 influence the reaction include alcohols such as methanol, ethanol, propanol, 2-propanol, butanol, isobutanol, tert-butanol and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; aliphatic hydrocarbons such as hexane, heptane and the like; 35 ethers such as diethyl ether, diisopropyl ether, tert-butylmethyl ether, tetrahydrofuran, dioxane,

dimethoxyethane and the like; esters such as methyl acetate, ethyl acetate, n-butyl acetate, tert-butyl acetate and the like; amides such as dimethylformamide, dimethylacetamide, N-methylpyrrolidone and the like.

- 5 Two or more of these solvents may be used upon mixing at a suitable ratio.

The reaction temperature is generally from -70°C to 150°C, preferably -20°C to 100°C.

- 10 The reaction time is generally from 0.1 to 100 hours, preferably from 0.1 to 40 hours.

The reduction reaction can be also conducted in the presence of a metal catalyst such as palladium-carbon, palladium black, palladium chloride, platinum oxide, platinum black, platinum-palladium, Raney-nickel, Raney-15 cobalt and the like, and a hydrogen source in a solvent that does not adversely influence the reaction.

The amount of the metal catalyst to be used is generally 0.001 to 1000 molar equivalents, preferably 0.01 to 100 molar equivalents, per compound (XIV).

- 20 Examples of the hydrogen source include hydrogen gas, formic acid, formic acid amine salt, phosphinate, hydrazine and the like.

- 25 The solvent that does not adversely influence the reaction is that employed for reduction using the aforementioned reducing agent.

The reaction temperature and reaction time are the same as those for reduction using the aforementioned reducing agent.

- 30 This reaction may be carried out in the presence of ammonia (e.g., aqueous ammonia, ammonia-ethanol and the like) as necessary. By reacting in the presence of ammonia, side reaction is suppressed and compound (I-af) can be produced in a high yield.

- 35 The thus-obtained compound (I-af) can be isolated and purified by a known separation and purification means, such as concentration, concentration under

reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like. It is also possible to subject a reaction mixture containing compound (I-af) to the next reaction 5 without isolating compound (I-af).

The compound (I-ad) is produced by reacting compound (I-af) and a metal cyanide.

Examples of the metal cyanide include potassium cyanide, sodium cyanide, zinc cyanide and the like.

10 The reaction is generally carried out in a solvent that does not adversely influence the reaction.

Examples of the solvent that does not adversely influence the reaction include amides such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone and the like; sulfoxides such as dimethyl sulfoxide and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether, dimethoxyethane and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile, propionitrile and the like; water and the like. Two or more of these solvents may be used upon mixing at a suitable ratio.

25 In this reaction, a catalyst may be used where necessary. Examples of the catalyst include transition metal compounds, such as rhodium, palladium-carbon, tetrakis(triphenylphosphine)palladium, tetrakis(tri-(2-toryl)phosphine)palladium, tetrakis(tri-(2-furyl)phosphine)palladium, bis(acetylacetone)nickel, dichlorobis(triphenylphosphine)nickel, bis(1,5-cyclooctadiene)nickel, bis(1,10-phenanthroline)nickel, Raney-nickel, Raney-cobalt and the like.

30 The amount of the metal cyanide to be used is generally 1 to 100 molar equivalents, preferably 1 to 10 molar equivalents, per compound (I-af).

The amount of the catalyst to be used is generally 0.00001 to 10 molar equivalents, preferably 0.001 to 1 molar equivalent, per compound (I-af).

The reaction temperature is generally from -10°C to 250°C, preferably 0°C to 150°C.

The reaction time is generally from 0.1 to 100 hours, preferably 0.1 to 40 hours.

The thus-obtained compound (I-ad) can be isolated and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

The compound (XVI) used as a starting material compound in Method I can be produced according to a method known *per se*.

In each of the aforementioned reactions, when the starting material compound has amino, carboxy, hydroxy or carbonyl as a substituent, a protecting group generally known in peptide chemistry and the like may be introduced into these groups. By removing the protecting group as necessary after the reaction, the objective compound can be obtained.

The amino-protecting group includes, for example, formyl, C₁₋₆ alkyl-carbonyl (e.g., acetyl, propionyl and the like), C₁₋₆ alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl and the like), benzoyl, C₇₋₁₃ aralkyl-carbonyl (e.g., benzylcarbonyl and the like), C₇₋₁₃ aralkyloxy-carbonyl (e.g., 30 benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl and the like), trityl, phthaloyl, N,N-dimethylaminomethylene, silyl (e.g., trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyldimethylsilyl, tert-butyltriethylsilyl and the like), C₂₋₆ alkenyl (e.g., 1-allyl and the like) and the like. These groups are optionally substituted by 1 to 3 halogen atom(s) (e.g.,

fluorine, chlorine, bromine, iodine and the like), C₁₋₆ alkoxy (e.g., methoxy, ethoxy, propoxy and the like) or nitro and the like.

The carboxy-protecting group is, for example, C₁₋₆ alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, tert-butyl and the like), C₇₋₁₃ aralkyl (e.g., benzyl and the like), phenyl, trityl, silyl (e.g., trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyldimethylsilyl, tert-butyldiethylsilyl and the like), C₂₋₆ alkenyl (e.g., 1-allyl and the like) and the like. These groups are optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine and the like), C₁₋₆ alkoxy (e.g., methoxy, ethoxy, propoxy and the like) or nitro and the like.

The hydroxy-protecting group is, for example, C₁₋₆ alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, tert-butyl and the like), phenyl, trityl, C₇₋₁₃ aralkyl (e.g., benzyl and the like), formyl, C₁₋₆ alkyl-carbonyl (e.g., acetyl, propionyl and the like), benzoyl, C₇₋₁₃ aralkyl-carbonyl (e.g., benzylcarbonyl and the like), 2-tetrahydropyranyl, 2-tetrahydrofuryl, silyl (e.g., trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyldimethylsilyl, tert-butyldiethylsilyl and the like), C₂₋₆ alkenyl (e.g., 1-allyl and the like) and the like. These groups are optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine and the like), C₁₋₆ alkyl (e.g., methyl, ethyl, propyl and the like), C₁₋₆ alkoxy (e.g., methoxy, ethoxy, propoxy and the like) or nitro and the like.

The carbonyl-protecting group is, for example, cyclic acetal (e.g., 1,3-dioxane and the like), non-cyclic acetal (e.g., di-C₁₋₆ alkyl acetal and the like) and the like.

Introduction and removal of these protecting groups can follow a method known per se, for example, a method described in Protective Groups in Organic Synthesis,

John Wiley and Sons (1980) and the like. For example, employed is a method using acid, base, UV light, hydrazine, phenyl hydrazine, sodium N-methyldithiocarbamate, tetrabutylammonium fluoride,

- 5 palladium acetate, trialkylsilyl halide (e.g., trimethylsilyl iodide, trimethylsilyl bromide and the like) and the like, reduction and the like.

When the starting material compound can form a salt in each of the aforementioned reactions, the compound in 10 the form of a salt may be used. The salt is, for example, the salt of compound (I) exemplified above.

When compound (I) contains an optical isomer, a stereoisomer, a positional isomer or a rotational isomer, these are also encompassed in compound (I), and can be 15 obtained as a single product according to a synthetic method and separation method known *per se*. For example, when compound (I) contains an optical isomer, an optical isomer resolved from this compound is also encompassed in compound (I).

20 The optical isomer can be produced by a method known *per se*. To be specific, an optically active synthetic intermediate is used, or the final racemate product is subjected to optical resolution according to a conventional method to give an optical isomer.

25 The method of optical resolution may be a method known *per se*, such as a fractional recrystallization method, a chiral column method, a diastereomer method and the like.

1) Fractional recrystallization method
30 A salt of a racemate with an optically active compound (e.g., (+)-mandelic acid, (-)-mandelic acid, (+)-tartaric acid, (-)-tartaric acid, (+)-1-phenethylamine, (-)-1-phenethylamine, cinchonine, (-)-cinchonidine, brucine and the like) is formed, which is 35 separated by a fractional recrystallization method, and a free optical isomer is obtained by a neutralization

step where desired.

2) Chiral column method

A racemate or a salt thereof is applied to a column for separation of an optical isomer (chiral column) to allow separation. In the case of a liquid chromatography, for example, a mixture of an optical isomer is applied to a chiral column such as ENANTIO-OVM (manufactured by Tosoh Corporation) or CHIRAL series (manufactured by Daicel Chemical Industries, Ltd.) and the like, and developed with water, various buffers (e.g., phosphate buffer) and organic solvents (e.g., ethanol, methanol, isopropanol, acetonitrile, trifluoroacetic acid, diethylamine and the like) solely or in admixture to separate the optical isomer. In the case of a gas chromatography, for example, a chiral column such as CP-Chirasil-Dex CB (manufactured by GL Sciences Inc.) and the like is used to allow separation.

3) Diastereomer method

A racemate mixture is prepared into a diastereomer mixture by chemical reaction with an optically active reagent, which is prepared into a homogeneous substance by a typical separation means (e.g., fractional recrystallization, chromatography method and the like) and the like, and subjected to a chemical treatment such as hydrolysis and the like to separate the optically active reagent moiety, whereby an optical isomer is obtained. For example, when compound (I) contains hydroxy or primary or secondary amino in a molecule, the compound and an optically active organic acid (e.g., MTPA [α -methoxy- α -(trifluoromethyl)phenylacetic acid], (-)-menthoxyacetic acid and the like) and the like are subjected to condensation to give an ester form or amide form diastereomer. When compound (I) has a carboxylic acid group, this compound and an optically active amine or an alcohol reagent are subjected to condensation to give an ester form or amide form diastereomer. The

separated diastereomer is converted to an optical isomer of the original compound by acid hydrolysis or base hydrolysis.

The compound (I) and a salt thereof may be in the 5 form of a crystal.

The crystal of compound (I) or a salt thereof (hereinafter sometimes to be referred to as crystal of the present invention) can be produced by crystallization of compound (I) or a salt thereof by a 10 crystallization method known per se.

Examples of the crystallization method include crystallization from a solution, crystallization from vapor, crystallization from a molten form and the like.

The "crystallization method from a solution" is 15 typically a method including shifting a non-saturation state to hyper-saturation state by varying factors involved in solubility of compounds (solvent composition, pH, temperature, ionic strength, oxidation-reduction state and the like) or the amount of solvent. To be 20 specific, for example, concentration method, annealing method, reaction method (diffusion method, electrolysis method), hydrothermal growth method, fusing agent method and the like can be mentioned. Examples of the solvent to be used include aromatic hydrocarbons (e.g., benzene, 25 toluene, xylene and the like), halogenated hydrocarbons (e.g., dichloromethane, chloroform and the like), saturated hydrocarbons (e.g., hexane, heptane, cyclohexane and the like), ethers (e.g., diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane and the 30 like), nitriles (e.g., acetonitrile and the like), ketones (e.g., acetone and the like), sulfoxides (e.g., dimethyl sulfoxide and the like), acid amides (e.g., N,N-dimethylformamide and the like), esters (e.g., ethyl acetate and the like), alcohols (e.g., methanol, ethanol, 35 isopropyl alcohol and the like), water and the like. These solvents are used alone or in combination of two

or more at a suitable ratio (e.g., 1:1 to 1:100 (volume ratio)).

The "crystallization method from vapor" is, for example, vaporization method (sealed tube method, gas stream method), gas phase reaction method, chemical transportation method and the like.

The "crystallization method from a molten form" is, for example, normal freezing method (Czockralski method, temperature gradient method, Bridgman method), zone melting method (zone leveling method, floating zone method), special growth method (VLS method, liquid phase epitaxy method) and the like.

Preferable examples of the crystallization method include a method including dissolving compound (I) or a salt thereof in a suitable solvent (e.g., alcohols such as methanol, ethanol etc., and the like) at a temperature of 20-120°C and cooling the resulting solution to a temperature not higher than the temperature of dissolution (e.g., 0-50°C, preferably 0-20°C) and the like.

The thus-obtained crystals of the present invention can be isolated by, for example, filtration and the like.

In the present specification, the melting point refers to that measured using, for example, micromelting point measuring apparatus (Yanako, MP-500D) or DSC (differential scanning calorimetry) device (SEIKO, EXSTAR6000), and the like.

In the present specification, moreover, a peak by powder X-ray diffraction refers to that measured using, for example, RINT2100 (Rigaku Industrial Corporation) and the like using Cu-K α 1 ray (tube voltage:40 KV; tube current: 50 mA) as a ray source.

In general, melting points and peaks by powder X-ray diffraction vary depending on measurement apparatuses, measurement conditions and the like. The crystal in the present specification may show a

different melting point or a peak by powder X-ray diffraction described in the present specification, as long as it is within general error range.

The crystal of the present invention is superior in physicochemical properties (e.g., melting point, solubility, stability and the like) and biological properties (e.g., pharmacokinetics (absorption, distribution, metabolism, excretion), efficacy expression and the like), and is extremely useful as a pharmaceutical agent.

The present invention is explained in more detail by the following Examples, Reference Examples, Experimental Examples and Formulation Examples. These do not limit the present invention and the present

invention can be modified within the range that does not deviate from the scope of the invention.

The abbreviations in Examples and Reference Examples mean the following.

s: singlet, d: doublet, t: triplet, q: quartet, dd: double doublet, dt: double triplet, m: multiplet, bs: broad singlet, tt: triple triplet, J: coupling constant, room temperature: 0-30°C

Examples

Example 1

3-(Aminomethyl)-4-butoxy-6-ethoxy-2-neopentyl-1(2H)-isoquinolinone hydrochloride
(1) A solution of 4-fluorophthalic anhydride (8.31 g, 50 mmol) and ethyl 2-(neopentylamino)acetate (10.40 g, 60 mmol) in tetrahydrofuran (50 ml) was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in N,N-dimethylformamide (50 ml), and potassium carbonate (6.91 g, 50 mmol) and ethyl iodide (4.8 ml, 60 mmol) were

added. The mixture was stirred at room temperature for 3 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and 5 concentrated under reduced pressure. The residue was dissolved in ethanol (50 ml) and 20% sodium ethoxide ethanol solution (34.04 g, 100 mmol) was added. The mixture was stirred at room temperature for 1 h. The reaction mixture was poured into 1N hydrochloric acid 10 (150 ml) and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography and the component eluted earlier was concentrated to 15 give ethyl 7-fluoro-4-hydroxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (5.12 g, 31.9%) as crystals.

Melting point 92-93°C.

Elemental analysis for C₁₇H₂₀NO₄F

20 Calculated: C, 63.54; H, 6.27; N, 4.36.
Found: C, 63.56; H, 6.19; N, 4.16.
¹H-NMR(CDCl₃) δ: 0.85 (9H, s), 1.47 (3H, t, J=7.1 Hz), 4.48 (2H, q, J=7.1 Hz), 4.54 (2H, bs), 7.42-7.52 (1H, m), 8.10 (1H, dd, J=2.7, 9.2 Hz), 8.17 (1H, dd, J=5.5, 9.2 25 Hz), 10.19 (1H, s).

The component eluted later was concentrated to give ethyl 6-fluoro-4-hydroxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (3.85 g, 24.0%) as crystals.

Melting point 115-115.5°C.

30 Elemental analysis for C₁₇H₂₀NO₄F
Calculated: C, 63.54; H, 6.27; N, 4.36.
Found: C, 63.54; H, 6.19; N, 4.11.
¹H-NMR(CDCl₃) δ: 0.85 (9H, s), 1.47 (3H, t, J=7.2 Hz), 4.49 (2H, q, J=7.2 Hz), 4.54 (2H, bs), 7.32-7.42 (1H, m), 35 7.72 (1H, dd, J=2.9, 9.2 Hz), 8.47 (1H, dd, J=5.5, 9.2 Hz), 10.70 (1H, s).

(2) To a solution of ethyl 6-fluoro-4-hydroxy-2-neopentyl-1-oxo-1,2-dihydro-3-isooquinolinecarboxylate (3.21 g, 10 mmol), 1-butanol (1.4 ml, 15 mmol) and tributylphosphine (5.0 ml, 20 mmol) in tetrahydrofuran (30 ml) was added 1,1'-azodicarbonylpiperidine (5.05 g, 20 mmol) and the mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography to give ethyl 4-butoxy-6-fluoro-2-neopentyl-1-oxo-1,2-dihydro-3-isooquinolinecarboxylate (3.55 g, 94.2%) as an oil.

¹H-NMR(CDCl₃) δ: 0.94 (9H, s), 1.01 (3H, t, J=7.4 Hz), 1.44 (3H, t, J=7.1 Hz), 1.48-1.59 (2H, m), 1.73-1.89 (2H, m), 3.94 (2H, t, J=6.5 Hz), 4.07 (2H, bs), 4.44 (2H, q, J=7.1 Hz), 7.21-7.31 (1H, m), 7.38 (1H, dd, J=2.5, 9.1 Hz), 8.45 (1H, dd, J=5.6, 8.8 Hz).

(3) To a solution of ethyl 4-butoxy-6-fluoro-2-neopentyl-1-oxo-1,2-dihydro-3-isooquinolinecarboxylate (3.40 g, 9 mmol) in tetrahydrofuran (20 ml) and ethanol (20 ml) was added sodium hydroxide (1.08 g, 27 mmol). The obtained mixture was refluxed under heating for 12 h. The reaction mixture was poured into water and acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 ml) and oxalyl chloride (0.9 ml, 10.8 mmol) and N,N-dimethylformamide (2 drops) were added thereto. The mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 ml). The obtained solution was added dropwise to a suspension of sodium tetrahydronborate (1.13 g, 30 mmol) in 1,2-dimethoxyethane (20 ml) at 0°C. The obtained mixture was stirred at 0°C for 1 h. The reaction mixture was poured

into 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography and the component eluted earlier was concentrated to give 4-butoxy-6-fluoro-3-hydroxymethyl-2-neopentyl-1(2H)-isoquinolinone (1.72 g, 57.1%) as crystals.

Melting point 143-143.5°C.

10 Elemental analysis for C₁₉H₂₆NO₃F

Calculated: C, 68.04; H, 7.81; N, 4.18.

Found: C, 67.85; H, 7.72; N, 4.20.

¹H-NMR(CDCl₃) δ: 0.96 (9H, s), 1.00 (3H, t, J=7.3 Hz), 1.50-1.68 (2H, m), 1.79-1.93 (2H, m), 2.46 (1H, bs), 15 3.88 (2H, t, J=6.6 Hz), 4.17 (2H, bs), 4.87 (2H, bs), 7.08-7.18 (1H, m), 7.24-7.30 (1H, m), 8.28-8.37 (1H, m).

The component eluted later was concentrated to give 4-butoxy-6-ethoxy-3-hydroxymethyl-2-neopentyl-1(2H)-isoquinolinone (0.51 g, 15.7%) as crystals.

20 Melting point 92.5-93.0°C.

Elemental analysis for C₂₁H₃₁NO₄

Calculated: C, 69.78; H, 8.64; N, 3.87.

Found: C, 69.84; H, 8.65; N, 3.68.

¹H-NMR(CDCl₃) δ: 0.95 (9H, s), 1.03 (3H, t, J=7.3 Hz), 1.48 (3H, t, J=7.0 Hz), 1.54-1.66 (2H, m), 1.79-1.89 (2H, m), 2.77 (1H, bs), 3.89 (2H, t, J=6.4 Hz), 4.13 (2H, q, J=7.0 Hz), 4.18 (2H, bs), 4.85 (2H, bs), 6.93-6.98 (2H, m), 8.17-8.22 (1H, m).

(4) To a solution of 4-butoxy-6-ethoxy-3-hydroxymethyl-

30 2-neopentyl-1(2H)-isoquinolinone (0.43 g, 1.2 mmol) in tetrahydrofuran (10 ml) and toluene (10 ml) was added thionyl chloride (0.18 ml, 2.4 mmol). The obtained mixture was refluxed under heating for 2 h. The reaction mixture was poured into saturated aqueous 35 sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried

over anhydrous magnesium sulfate and concentrated under reduced pressure to give 4-butoxy-6-ethoxy-3-chloromethyl-2-neopentyl-1(2H)-isoquinolinone (0.41 g, 91.1%) as an oil.

- 5 ¹H-NMR(CDCl₃) δ: 0.98 (9H, s), 1.04 (3H, t, J=7.3 Hz), 1.48 (3H, t, J=7.0 Hz), 1.55-1.70 (2H, m), 1.81-1.91 (2H, m), 3.95 (2H, t, J=6.5 Hz), 4.10 (2H, bs), 4.15 (2H, q, J=7.0 Hz), 4.87 (2H, bs), 7.05-7.30 (2H, m), 8.34 (1H, d, J=9.4 Hz).
- 10 (5) A solution of 4-butoxy-6-ethoxy-3-chloromethyl-2-neopentyl-1(2H)-isoquinolinone (0.38 g, 1 mmol) and potassium phthalimide (0.28 g, 1.5 mmol) in N,N-dimethylformamide (10 ml) was stirred at room temperature for 6 h. The reaction mixture was poured
- 15 into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 2-{{(4-butoxy-6-ethoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isooquinolinyl)methyl}-1H-isooindole-1,3(2H)-dione (0.48 g, 98.0%) as an amorphous.

Elemental analysis for C₂₉H₃₄N₂O₅

Calculated: C, 71.00; H, 6.99; N, 5.71.

25 Found: C, 71.41; H, 7.15; N, 5.64.

¹H-NMR(CDCl₃) δ: 1.00 (9H, s), 1.01 (3H, t, J=7.3 Hz), 1.48 (3H, t, J=7.0 Hz), 1.50-1.61 (2H, m), 1.81-1.94 (2H, m), 3.99 (2H, bs), 4.02 (2H, t, J=6.8 Hz), 4.15 (2H, q, J=7.0 Hz), 5.07 (2H, s), 7.02-7.10 (2H, m), 7.69-7.80

30 (1H, m); 8.31 (1H, d, J=8.8 Hz).

(6) To a solution of 2-{{(4-butoxy-6-ethoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isooquinolinyl)methyl}-1H-isooindole-1,3(2H)-dione (0.43 g, 1.2 mmol) in ethanol (20 ml) was added hydrazine monohydrate (0.13 ml, 2.7 mmol). The

35 obtained mixture was refluxed under heating for 2 h. The reaction mixture was poured into saturated aqueous

sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in 5 tetrahydrofuran (20 ml) and di-t-butyl dicarbonate (0.31 g, 1.4 mmol) was added thereto. The obtained mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over 10 anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl (4-butoxy-6-ethoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl carbamate (0.36 g, 87.8%) as 15 crystals.

Melting point 138-139°C.

Elemental analysis for C₂₆H₄₀N₂O₅

Calculated: C, 67.80; H, 8.75; N, 6.08.

Found: C, 67.76; H, 8.91; N, 5.87.

20 ¹H-NMR(CDCl₃) δ: 0.99 (9H, s), 1.03 (3H, t, J=7.0 Hz), 1.45 (9H, s); 1.49 (3H, t, J=7.0 Hz), 1.52-1.64 (2H, m), 1.79-1.91 (2H, m), 3.96 (2H, t, J=6.4 Hz), 4.10 (2H, bs), 4.15 (2H, q, J=7.0 Hz), 4.55 (2H, d, J=5.6 Hz), 4.67 (1H, bs), 7.02-7.08 (2H, m), 8.29-8.34 (1H, m).

25 (7) To a solution of tert-butyl (4-butoxy-6-ethoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.28 g, 0.6 mmol) in ethyl acetate (5 ml) was added a solution of 4N hydrogen chloride in ethyl acetate (5 ml), and the obtained 30 solution was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the precipitated crystals were recrystallized from methanol-diisopropyl ether to give 3-(aminomethyl)-4-butoxy-6-ethoxy-2-neopentyl-1(2H)-isoquinolinone 35 hydrochloride (0.23 g, 95.8%) as crystals.

Melting point 195.5-201°C.

Elemental analysis for C₂₁H₃₃N₂O₃Cl 1/4H₂O

Calculated: C, 62.83; H, 8.41; N, 6.98.

Found: C, 62.79; H, 8.52; N, 6.72.

¹H-NMR(DMSO-d₆) δ:0.90 (9H, s), 1.00 (3H, t, J=7.3 Hz),

5 1.41 (3H, t, J=7.0 Hz), 1.51-1.63 (2H, m), 1.77-1.91 (2H, m), 3.93 (2H, t, J=6.4 Hz), 4.09 (2H, bs), 4.20 (2H, q, J=7.0 Hz), 4.22 (2H, s), 7.07 (1H, d, J=2.2 Hz), 7.18 (1H, dd, J=2.2, 8.8 Hz), 8.18 (1H, d, J=8.8 Hz), 8.56 (3H, bs).

10 Example 2

3-(Aminomethyl)-4-butoxy-7-fluoro-2-neopentyl-1(2H)-isoquinolinone hydrochloride

(1) To a solution of ethyl 7-fluoro-4-hydroxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate

15 (5.12 g, 31.9%) (from Example 1(1), 3.21 g, 10 mmol), 1-butanol (1.4 ml, 15 mmol) and tributylphosphine (5.0 ml, 20 mmol) in tetrahydrofuran (30 ml) was added 1,1'-(azodicarbonyl)dipiperidine (5.05 g, 20 mmol) and the mixture was stirred at room temperature for 3 h. The
20 reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography to give ethyl 4-butoxy-7-fluoro-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (3.55 g, 94.2%) as an oil.

25 ¹H-NMR(CDCl₃) δ:0.94 (9H, s), 1.01 (3H, t, J=7.1 Hz), 1.44 (3H, t, J=7.1 Hz), 1.51-1.63 (2H, m), 1.73-1.87 (2H, m), 3.95 (2H, t, J=6.4 Hz), 4.11 (2H, bs), 4.43 (2H, q, J=7.1 Hz), 7.40-7.50 (1H, m), 7.79 (1H, dd, J=5.2, 8.8 Hz), 8.09 (1H, dd, J=2.8, 9.4 Hz).

30 (2) To a solution of 4-butoxy-7-fluoro-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (3.40 g, 9 mmol) in tetrahydrofuran (20 ml) and ethanol (20 ml) was added sodium hydroxide (1.08 g, 27 mmol). The obtained mixture was refluxed under heating for 3 h. The
35 reaction mixture was poured into water, and, after making the mixture acidic with 1N hydrochloric acid,

extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from tetrahydrofuran-
5 diisopropyl ether to give 4-butoxy-7-fluoro-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (3.04 g, 96.8%) as crystals.

Melting point 184-185°C.

Elemental analysis for C₁₉H₂₄NO₄F

10 Calculated: C, 65.31; H, 6.92; N, 4.01.

Found: C, 65.49; H, 7.11; N, 3.77.

¹H-NMR(CDCl₃) δ: 0.94 (9H, s), 0.99 (3H, t, J=7.5 Hz), 1.45-1.64 (2H, m), 1.77-1.91 (2H, m), 4.03 (2H, t, J=6.6 Hz), 4.30 (2H, bs), 5.67 (1H, bs), 7.42-7.52 (1H, m);
15 7.80 (1H, dd, J=5.2, 8.8 Hz), 8.09 (1H, dd, J=2.6, 9.2 Hz).

(3) 4-Butoxy-7-fluoro-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (2.97 g, 8.5 mmol) was dissolved in tetrahydrofuran (30 ml) and oxalyl chloride
20 (0.9 ml, 10.2 mmol) and N,N-dimethylformamide (2 drops) were added thereto. The mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in tetrahydrofuran (20 ml). The obtained

25 solution was added dropwise to sodium tetrahydroborate (1.13 g, 30 mmol) in dimethoxyethane (20 ml) at 0°C. The obtained mixture was stirred at 0°C for 1 h. The reaction mixture was poured into 1N hydrochloric acid and extracted with ethyl acetate. The extract was

30 washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from tetrahydrofuran-diisopropyl ether to give 4-butoxy-7-fluoro-3-hydroxymethyl-2-neopentyl-1(2H)-isoquinolinone
35 (2.52 g, 88.4%) as crystals.

Melting point 149-150°C.

Elemental analysis for C₁₉H₂₆NO₃F

Calculated: C, 68.04; H, 7.81; N, 4.18.

Found: C, 67.80; H, 8.00; N, 4.19.

¹H-NMR(CDCl₃) δ: 0.95 (9H, s), 1.04 (3H, t, J=7.1 Hz),

5 1.50-1.69 (2H, m), 1.71-1.94 (2H, m), 2.93 (1H, bs),
3.91 (2H, t, J=6.6 Hz), 4.21 (2H, bs), 4.87 (2H, bs),
7.27-7.36 (1H, m), 7.65 (1H, dd, J=5.0, 8.8 Hz), 7.86
(1H, dd, J=2.4, 9.2 Hz).

(4) To a solution of 4-butoxy-7-fluoro-3-hydroxymethyl-

10 2-neopentyl-1(2H)-isoquinolinone (2.35 g, 7 mmol) in tetrahydrofuran (10 ml) and toluene (10 ml) was added thionyl chloride (1.0 ml, 14 mmol) and the obtained mixture was refluxed under heating for 2 h. The reaction mixture was poured into saturated aqueous

15 sodium hydrogen carbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 4-butoxy-7-fluoro-3-chloromethyl-2-neopentyl-1(2H)-isoquinolinone (2.04 g,

20 82.6%) as an oil.

¹H-NMR(CDCl₃) δ: 0.99 (9H, s), 1.04 (3H, t, J=7.3 Hz),
1.51-1.69 (2H, m), 1.81-1.91 (2H, m), 3.94 (2H, t, J=6.4 Hz), 4.20 (2H, bs), 4.88 (2H, bs), 7.38-7.48 (1H, m),
7.75 (1H, dd, J=5.0, 8.8 Hz), 8.09 (1H, dd, J=2.6, 9.0

25 Hz).

(5) A solution of 4-butoxy-7-fluoro-3-chloromethyl-2-neopentyl-1(2H)-isoquinolinone (1.95 g, 5.5 mmol) and potassium phthalimide (1.54 g, 8.3 mmol) in N,N-dimethylformamide (20 ml) was stirred at room

30 temperature for 6 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were

35 recrystallized from ethyl acetate-diisopropyl ether to give 2-{(4-butoxy-7-fluoro-2-neopentyl-1-oxo-1,2-

dihydro-3-isoquinolinyl)methyl}-1H-isoindole-1,3(2H)-dione (2.46 g, 96.5%) as crystals.

Melting point 155-156°C.

Elemental analysis for C₂₇H₂₉N₂O₄F

⁵ Calculated: C, 69.81; H, 6.29; N, 6.03.

Found: C, 69.84; H, 6.17; N, 5.88.

¹H-NMR(CDCl₃) δ:1.00 (3H, t, J=7.3 Hz), 1.01 (9H, s), 1.45-1.62 (2H, m), 1.81-1.95 (2H, m), 4.02 (2H, t, J=6.7 Hz), 4.13 (2H, bs), 5.07 (2H, bs), 7.36-7.45 (1H, m),

¹⁰ 7.69-7.83 (5H, m), 8.05 (1H, dd, J=2.6, 9.4 Hz).

(6) To a suspension of 2-((4-butoxy-7-fluoro-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl}-1H-isoindole-1,3(2H)-dione (2.32 g, 5 mmol) in ethanol (20 ml) was added hydrazine monohydrate (0.73 ml, 15 mmol).

¹⁵ The obtained mixture was refluxed under heating for 2 h. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in

tetrahydrofuran (20 ml) and di-t-butyl dicarbonate (1.64 g, 7.5 mmol) was added thereto. The obtained mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate.

²⁵ The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give tert-butyl (4-butoxy-7-fluoro-2-neopentyl-1-oxo-

³⁰ 1,2-dihydro-3-isoquinolinyl)methylcarbamate (1.93 g, 88.9%) as crystals.

Melting point 149-150°C.

Elemental analysis for C₂₄H₃₅N₂O₄F

Calculated: C, 66.34; H, 8.12; N, 6.45.

³⁵ Found: C, 66.33; H, 8.14; N, 6.33.

¹H-NMR(CDCl₃) δ:0.99 (9H, s), 1.03 (3H, t, J=7.4 Hz),

1.45 (9H, s), 1.52-1.67 (2H, m), 1.79-1.93 (2H, m), 3.86 (2H, t; J=6.4 Hz), 4.13 (2H, bs), 4.57 (2H, d, J=5.6 Hz), 4.68 (1H, bs), 7.36-7.45 (1H, m), 7.70 (1H, dd, J=5.1, 8.7 Hz), 8.05 (1H, dd, J=2.7, 9.3 Hz).

- 5 (7) To a solution of tert-butyl (4-butoxy-7-fluoro-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (1.74 g, 4 mmol) in ethyl acetate (5 ml) was added a solution of 4N hydrogen chloride in ethyl acetate (5 ml), and the obtained
10 solution was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure and the precipitated crystals were recrystallized from methanol - diisopropyl ether to give 3-(aminomethyl)-4-butoxy-7-fluoro-2-neopentyl-1(2H)-isoquinolinone
15 hydrochloride (1.42 g, 95.9%) as crystals.
Melting point 198-199°C.
Elemental analysis for C₁₉H₂₈N₂O₂ClF 1/2H₂O
Calculated: C, 60.07; H, 7.69; N, 7.37.
Found: C, 60.33; H, 7.57; N, 7.42.
20 ¹H-NMR(DMSO-d₆) δ: 0.91 (9H, s), 0.99 (3H, t, J=7.4 Hz), 1.45-1.64 (2H, m), 1.78-1.92 (2H, m), 3.94 (2H, t, J=6.4 Hz), 4.12 (2H, bs), 4.25 (2H, bs), 7.70-7.80 (1H, m), 7.87 (1H, dd, J=5.4, 9.0 Hz), 7.95 (1H, dd, J=2.5, 9.5 Hz), 8.60 (3H, bs).

25 Example 3

- 3-(Aminomethyl)-4-butoxy-6-fluoro-2-neopentyl-1(2H)-isoquinolinone hydrochloride
(1) To a solution of 4-butoxy-6-fluoro-3-hydroxymethyl-2-neopentyl-1(2H)-isoquinolinone (from Example 1(3),
30 1.68 g, 5 mmol) in tetrahydrofuran (10 ml) and toluene (10 ml) was added thionyl chloride (0.73 ml, 10 mmol), and the resulting mixture was refluxed under heating for 2 h. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution and extracted
35 with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated

under reduced pressure to give 4-butoxy-6-fluoro-3-chloromethyl-2-neopentyl-1(2H)-isoquinolinone (1.62 g, 92.0%) as an oil.

¹H-NMR(CDCl₃) δ: 0.98 (9H, s), 1.04 (3H, t, J=7.4 Hz),
5 1.51-1.69 (2H, m), 1.81-1.95 (2H, m), 3.94 (2H, t, J=6.6 Hz), 4.17 (2H, bs), 4.87 (2H, bs), 7.12-7.30 (1H, m), 7.35 (1H, dd, J=2.6, 9.6 Hz), 8.09 (1H, dd, J=5.8, 9.0 Hz).

(2) A solution of 4-butoxy-6-fluoro-3-chloromethyl-2-neopentyl-1(2H)-isoquinolinone (1.59 g, 4.5 mmol) and potassium phthalimide (1.26 g, 6.8 mmol) in N,N-dimethylformamide (20 ml) was stirred at room temperature for 6 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give 2-{(4-butoxy-6-fluoro-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl}-1H-isoindole-1,3(2H)-dione (1.81 g, 86.6%) as crystals.

Melting point 162-164°C.

Elemental analysis for C₂₇H₂₉N₂O₄F

Calculated: C, 69.81; H, 6.29; N, 6.03.

25 Found: C, 69.47; H, 6.10; N, 6.02.

¹H-NMR(CDCl₃) δ: 1.00 (9H, s), 1.01 (3H, t, J=7.3 Hz), 1.48-1.62 (2H, m), 1.81-1.95 (2H, m), 4.01 (2H, t, J=6.8 Hz), 4.04 (2H, bs), 5.07 (2H, bs), 7.13-7.23 (1H, m), 7.34 (1H, dd, J=2.4, 9.8 Hz), 7.70-7.86 (4H, m), 8.42 (1H, dd, J=5.6, 8.8 Hz).

(3) To a suspension of 2-{(4-butoxy-6-fluoro-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl}-1H-isoindole-1,3(2H)-dione (1.71 g, 3.7 mmol) in ethanol (20 ml) was added hydrazine monohydrate (0.54 ml, 11.1 mmol). The resulting mixture was refluxed under heating for 2 h. The reaction mixture was poured into saturated

aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in

5 tetrahydrofuran (20 ml) and di-t-butyl dicarbonate (1.22 g, 5.6 mmol) was added thereto. The obtained mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over

10 anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting crystals were recrystallized from ethyl acetate - n-hexane to give tert-butyl (4-butoxy-6-fluoro-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (1.35 g, 83.9%)

15 as crystals.

Melting point 168-169°C.

Elemental analysis for C₂₄H₃₅N₂O₄F

Calculated: C, 66.34; H, 8.12; N, 6.45.

Found: C, 66.18; H, 8.26; N, 6.34.

20 ¹H-NMR(CDCl₃) δ: 1.00 (9H, s), 1.04 (3H, t, J=7.0 Hz), 1.45 (9H, s), 1.52-1.67 (2H, m), 1.79-1.93 (2H, m), 3.85 (2H, t, J=6.4 Hz), 4.11 (2H, bs), 4.56 (2H, d, J=5.2 Hz), 4.68 (1H, bs), 7.14-7.24 (1H, m), 7.30 (1H, dd, J=2.6, 10.0 Hz), 8.42 (1H, dd, J=5.4, 8.8 Hz).

25 (4) To a solution of tert-butyl (4-butoxy-6-fluoro-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (1.22 g, 2.8 mmol) in ethyl acetate (5 ml) was added a solution of 4N hydrogen chloride in ethyl acetate (5 ml), and the obtained

30 solution was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the precipitated crystals were recrystallized from methanol-diisopropyl ether to give 3-(aminomethyl)-4-butoxy-6-fluoro-2-neopentyl-1(2H)-isoquinoline

35 hydrochloride (1.01 g, 98.1%) as crystals.

Melting point 195.5-201°C.

Elemental analysis for C₁₉H₂₈N₂O₂ClF 1/4H₂O

Calculated: C, 62.83; H, 8.41; N, 6.98.

Found: C, 62.79; H, 8.52; N, 6.72.

¹H-NMR(DMSO-d₆) δ:0.90 (9H, s), 1.00 (3H, t, J=7.3 Hz),

5 1.41 (3H, t, J=7.0 Hz), 1.51-1.63 (2H, m), 1.77-1.91 (2H, m), 3.93 (2H, t, J=6.4 Hz), 4.09 (2H, bs), 4.20 (2H, q, J=7.0 Hz), 4.22 (2H, s), 7.07 (1H, d, J=2.2 Hz), 7.18 (1H, dd, J=2.2, 8.8 Hz), 8.18 (1H, d, J=8.8 Hz), 8.56 (3H, bs).

10 Example 4

3-(Aminomethyl)-6-chloro-4-methoxy-2-methyl-1(2H)-isoquinolinone hydrochloride

(1) To a solution of 4-chlorophthalic anhydride (9.13 g, 50 mmol) in tetrahydrofuran (50 ml) was added 28% sodium methoxide-methanol solution (11.6 ml, 60 mmol), and the mixture was stirred at room temperature for 30 min. The reaction mixture was poured into water, and, after making the mixture acidic with 1N hydrochloric acid, extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (100 ml) and oxalyl chloride (5.2 ml, 60 mmol) and N,N-dimethylformamide (3 drops) were added thereto. The mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in N,N-dimethylacetamide (100 ml). To the obtained solution was added ethyl sarcosinate hydrochloride (9.22 g, 60 mmol). The obtained mixture was stirred at room temperature for 2 h. The reaction mixture was poured into 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in ethanol (100 ml) and 20% sodium ethoxide ethanol solution (27.2 g, 80 mmol) was added. The

mixture was stirred at room temperature for 1 h. The reaction mixture was poured into 1N hydrochloric acid (100 ml) and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography and the component eluted earlier was concentrated to give ethyl 7-chloro-4-hydroxy-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (2.24 g, 20.9%) as crystals.

Melting point 109-110°C.

Elemental analysis for $C_{13}H_{12}NO_4Cl$

Calculated: C, 55.43; H, 4.29; N, 4.97.

Found: C, 55.54; H, 4.22; N, 5.12.

¹⁵ 1H -NMR(CDCl₃) δ: 1.46 (3H, t, J=7.0 Hz), 3.68 (3H, s), 4.50 (2H, q, J=7.0 Hz), 7.70 (1H, dd, J=2.0, 8.6 Hz); 8.09 (1H, d, J=8.6 Hz), 8.43 (1H, d, J=2.0 Hz), 11.25 (1H, s).

The component eluted later was concentrated to give ²⁰ ethyl 6-chloro-4-hydroxy-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (2.82 g, 26.4%) as crystals.

Melting point 110-111°C.

Elemental analysis for $C_{13}H_{12}NO_4Cl$

Calculated: C, 55.43; H, 4.29; N, 4.97.

²⁵ Found: C, 55.49; H, 4.30; N, 5.11.

1H -NMR(CDCl₃) δ: 1.46 (3H, t, J=7.0 Hz), 3.68 (3H, s), 4.50 (2H, q, J=7.0 Hz), 7.63 (1H, dd, J=1.9, 8.7 Hz), 8.17 (1H, d, J=1.9 Hz), 8.38 (1H, d, J=8.7 Hz), 11.16 (1H, s).

³⁰ (2) A suspension of ethyl 6-chloro-4-hydroxy-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (1.41 g, 5 mmol), methyl iodide (0.47 ml, 7.5 mmol) and potassium carbonate (1.04 g, 7.5 mmol) in N,N-dimethylformamide (10 ml) was stirred at room temperature for 4 h. The ³⁵ reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column

chromatography to give ethyl 6-chloro-4-methoxy-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (1.11 g, 75.5%) as crystals.

Melting point 122-123°C.

⁵ Elemental analysis for C₁₄H₁₄NO₄Cl

Calculated: C, 56.86; H, 4.77; N, 4.74.

Found: C, 56.85; H, 4.76; N, 4.57.

¹H-NMR(CDCl₃) δ: 1.45 (3H, t, J=7.2 Hz), 3.52 (3H, s), 3.89 (3H, s), 4.49 (2H, q, J=7.2 Hz), 7.51 (1H, dd,

¹⁰ J=2.2, 8.8 Hz), 7.74 (1H, d, J=2.2 Hz), 8.38 (1H, d, J=8.8 Hz).

(3) To a solution of ethyl 6-chloro-4-methoxy-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (1.03 g, 3.5 mmol) in tetrahydrofuran (10 ml) and ethanol (10 ml) was

¹⁵ added 1N sodium hydroxide (5 ml). The obtained mixture was refluxed under stirring at 50°C for 3 h. The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diethyl ether to give 6-chloro-4-methoxy-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (0.72 g, 77.4%) as crystals.

²⁵ Melting point 216-217°C.

Elemental analysis for C₁₂H₁₀NO₄Cl

Calculated: C, 53.85; H, 3.77; N, 5.23.

Found: C, 53.78; H, 3.74; N, 5.03.

¹H-NMR(CDCl₃) δ: 3.58 (3H, s), 3.91 (3H, s), 4.78 (1H, bs), ³⁰ 7.49 (1H, dd, J=2.0, 8.6 Hz), 7.75 (1H, d, J=2.0 Hz), 8.36 (1H, d, J=8.6 Hz).

(4) 6-Chloro-4-methoxy-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (0.67 g, 2.5 mmol) was dissolved in tetrahydrofuran (10 ml) and oxalyl chloride ³⁵ (0.26 ml, 3 mmol) and N,N-dimethylformamide (2 drops) were added thereto. The mixture was stirred at room

temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (10 ml). The obtained solution was added dropwise to a suspension of sodium

5 tetrahydroborate (0.33 g, 8.8 mmol) in 1,2-dimethoxyethane (20 ml) at 0°C. The obtained mixture was stirred at 0°C for 1 h, and the reaction mixture was poured into 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried 10 over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate-diisopropyl ether to give 6-chloro-3-hydroxymethyl-4-methoxy-2-methyl-1(2H)-isoquinolinone (0.42 g, 66.7%) as crystals.

15 Melting point 195-196°C.

Elemental analysis for C₁₂H₁₂NO₃Cl

Calculated: C, 56.81; H, 4.77; N, 5.52.

Found: C, 56.69; H, 4.88; N, 5.44.

¹H-NMR(CDCl₃) δ: 2.70 (1H, bs), 3.71 (3H, s), 3.82 (3H, s),

20 4.82 (2H, s), 7.40 (1H, dd, J=2.0, 8.6 Hz), 7.61 (1H, d, J=2.0 Hz), 8.26 (1H, d, J=8.6 Hz).

(5) To a solution of 6-chloro-3-hydroxymethyl-4-methoxy-2-methyl-1(2H)-isoquinolinone (0.76 g, 3 mmol) in tetrahydrofuran (20 ml) was added thionyl chloride (0.26

25 ml, 3.6 mmol). The obtained mixture was refluxed under heating for 2 h. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution, extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and

30 concentrated under reduced pressure to give 6-chloro-3-chloromethyl-4-methoxy-2-methyl-1(2H)-isoquinolinone (0.73 g, 90.1%) as crystals.

¹H-NMR(CDCl₃) δ: 3.73 (3H, s), 3.93 (3H, s), 4.80 (2H, s), 7.49 (1H, dd, J=2.0, 8.6 Hz), 7.74 (1H, d, J=2.0 Hz),

35 8.38 (1H, d, J=8.6 Hz).

(6) A solution of 6-chloro-3-chloromethyl-4-methoxy-2-

methyl-1(2H)-isoquinolinone (0.81 g, 3 mmol) and potassium phthalimide (0.83 g, 4.5 mmol) in N,N-dimethylformamide (20 ml) was stirred at room temperature for 4 h. The reaction mixture was poured
5 into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 2-{(6-chloro-4-
10 methoxy-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl}-1H-isoindole-1,3(2H)-dione (0.59 g, 51.8%) as crystals.
Melting point 248-249°C.
Elemental analysis for C₂₀H₁₅N₂O₄Cl
15 Calculated: C, 62.75; H, 3.95; N, 7.32.
Found: C, 62.73; H, 3.94; N, 7.32.
¹H-NMR(CDCl₃) δ: 3.61 (3H, s), 3.96 (3H, s), 5.07 (2H, s),
7.45 (1H, dd, J=2.0, 8.6 Hz), 7.73-7.88 (5H, m), 8.36
(1H, d, J=8.6 Hz).
20 (7) To a solution of 2-{(6-chloro-4-methoxy-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl}-1H-isoindole-1,3(2H)-dione (0.38 g, 1 mmol) in ethanol (10 ml) and tetrahydrofuran (10 ml) was added hydrazine monohydrate (0.14 ml, 3 mmol). The obtained mixture was refluxed
25 under heating for 2 h. The reaction mixture was poured into saturated aqueous sodium hydrogen carbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. To the
30 residue was added a solution of 4N hydrogen chloride in ethyl acetate (2 ml), and the precipitated crystals were recrystallized from methanol-diethyl ether to give 3-(aminomethyl)-6-chloro-4-methoxy-2-methyl-1(2H)-isoquinolinone hydrochloride (0.08 g, 28.6%) as crystals.
35 Melting point 236-237°C.
Elemental analysis for C₁₂H₁₄N₂O₂Cl₂

Calculated: C, 49.84; H, 4.88; N, 9.69.

Found: C, 49.67; H, 4.71; N, 9.48.

¹H-NMR(DMSO-d₆) δ:3.61 (3H, s), 3.85 (3H, s), 4.24 (2H, s), 7.66 (1H, dd, J=2.0, 8.6 Hz), 7.81 (1H, d, J=2.0 Hz),

⁵ 8.28 (1H, d, J=8.6 Hz), 8.75 (3H, bs).

Example 5

3-(Aminomethyl)-7-chloro-4-methoxy-2-methyl-1(2H)-isoquinolinone hydrochloride

(1) Ethyl 7-chloro-4-methoxy-2-methyl-1-oxo-1,2-dihydro-

¹⁰ 3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 4 (2))

Melting point 114-115°C.

Elemental analysis for C₁₄H₁₄NO₄Cl

Calculated: C, 56.86; H, 4.77; N, 4.74.

Found: C, 56.77; H, 4.74; N, 4.64.

¹H-NMR(CDCl₃) δ:1.45 (3H, t, J=7.1 Hz), 3.53 (3H, s), 3.89 (3H, s), 4.49 (2H, q, J=7.1 Hz), 7.67 (1H, dd, J=2.0, 8.6 Hz), 7.74 (1H, d, J=8.0 Hz), 8.38 (1H, d, J=2.0 Hz).

²⁰ (2) 7-Chloro-4-methoxy-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))

Melting point 163-164°C.

Elemental analysis for C₁₂H₁₀NO₄Cl

²⁵ Calculated: C, 53.85; H, 3.77; N, 5.23.

Found: C, 53.78; H, 3.74; N, 5.03.

¹H-NMR(CDCl₃) δ:3.60 (3H, s), 3.91 (3H, s), 7.66 (1H, dd, J=2.2, 8.8 Hz), 7.76 (1H, d, J=2.2 Hz), 8.40 (1H, d, J=2.2 Hz).

³⁰ (3) 7-Chloro-3-hydroxymethyl-4-methoxy-2-methyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))

Melting point 151-152°C.

Elemental analysis for C₁₂H₁₂NO₃Cl 1/4H₂O

³⁵ Calculated: C, 55.83; H, 4.88; N, 5.43.

Found: C, 55.88; H, 4.84; N, 5.55.

¹H-NMR(CDCl₃) δ: 2.57 (1H, bs), 3.73 (3H, s), 3.84 (3H, s), 4.83 (2H, s), 7.59 (1H, dd, J=2.0, 8.6 Hz), 7.66 (1H, d, J=8.6 Hz), 8.33 (1H, d, J=2.0 Hz).

(4) 7-Chloro-3-chloromethyl-4-methoxy-2-methyl-1(2H)-

5 isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

¹H-NMR(CDCl₃) δ: 3.74 (3H, s), 3.93 (3H, s), 4.81 (2H, s), 7.66 (1H, dd, J=2.2, 8.6 Hz), 7.66 (1H, d, J=8.6 Hz), 8.33 (1H, d, J=2.2 Hz).

10 (5) 2-{(7-Chloro-4-methoxy-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl}-1H-isoindole-1,3(2H)-dione
(synthesized according to the method similar to that in Example 4 (6))

Melting point 262-263°C.

15 Elemental analysis for C₂₀H₁₅N₂O₄Cl

Calculated: C, 62.75; H, 3.95; N, 7.32.

Found: C, 62.41; H, 3.91; N, 7.20.

¹H-NMR(CDCl₃) δ: 3.56 (3H, s), 3.82 (3H, s), 5.02 (2H, s), 7.81-7.86 (6H, m), 8.18 (1H, s).

20 (6) 3-(Aminomethyl)-7-chloro-4-methoxy-2-methyl-1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 4 (7)).

Melting point 225-226°C.

Elemental analysis for C₁₂H₁₄N₂O₂Cl₂

25 Calculated: C, 49.84; H, 4.88; N, 9.69.

Found: C, 49.82; H, 4.88; N, 10.12.

¹H-NMR(DMSO-d₆) δ: 3.62 (3H, s), 3.84 (3H, s), 4.23 (2H, d, J=4.4 Hz), 7.83-7.88 (2H, m), 8.22 (1H, d, J=0.8 Hz), 8.72 (3H, bs).

30 Example 6

3-(Aminomethyl)-6-chloro-4-isopropoxy-2-methyl-1(2H)-isoquinolinone hydrochloride

(1) Ethyl 6-chloro-4-isopropoxy-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according

35 to the method similar to that in Example 4 (2))

Melting point 66-67°C.

Elemental analysis for C₁₆H₁₈NO₄Cl

Calculated: C, 59.35; H, 5.60; N, 4.33.

Found: C, 59.22; H, 5.56; N, 4.33.

¹H-NMR(CDCl₃) δ:1.32 (6H, d, J=6.2 Hz), 1.45 (3H, t,

5 J=7.2 Hz), 3.52 (3H, s), 4.28-4.40 (1H, m), 4.47 (2H, q, J=7.2 Hz), 7.50 (1H, dd, J=2.0, 8.6 Hz), 7.75 (1H, d, J=2.0 Hz), 8.37 (1H, d, J=8.6 Hz).

(2) 6-Chloro-4-isopropoxy-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to

10 the method similar to that in Example 4 (3))

Melting point 229-230°C.

Elemental analysis for C₁₄H₁₄NO₄Cl

Calculated: C, 56.86; H, 4.77; N, 4.74.

Found: C, 56.86; H, 4.79; N, 4.48.

15 ¹H-NMR(CDCl₃) δ:1.34 (6H, d, J=6.2 Hz), 3.60 (3H, s); 4.34-4.46 (1H, m), 7.48 (1H, dd, J=2.2, 8.4 Hz), 7.77 (1H, d, J=2.2 Hz), 8.36 (1H, d, J=8.4 Hz).

(3) 6-Chloro-3-hydroxymethyl-4-isopropoxy-2-methyl-1(2H)-isoquinolinone (synthesized according to the

20 method similar to that in Example 4 (4))

Melting point 146-147°C.

Elemental analysis for C₁₄H₁₆NO₃Cl

Calculated: C, 59.68; H, 5.72; N, 4.97.

Found: C, 59.43; H, 5.70; N, 5.06.

25 ¹H-NMR(CDCl₃) δ:1.35 (6H, d, J=6.2 Hz), 2.34 (1H, bs), 3.74 (3H, s), 4.12-4.24 (1H, m), 4.83 (2H, d, J=4.8 Hz), 7.41 (1H, d, J=8.6 Hz), 7.61 (1H, s), 8.30 (1H, d, J=8.6 Hz).

(4) 2-[(6-Chloro-4-isopropoxy-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl]-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

Melting point 175-176°C.

Elemental analysis for C₂₂H₁₉N₂O₄Cl 1/2H₂O

35 Calculated: C, 62.93; H, 4.80; N, 6.67.

Found: C, 62.78; H, 4.65; N, 6.41.

¹H-NMR(CDCl₃) δ: 1.41 (6H, d, J=5.8 Hz), 3.60 (3H, s), 4.27-4.39 (1H, m), 5.08 (2H, s), 7.43 (1H, dd, J=2.0, 8.6 Hz), 7.68-7.90 (5H, m), 8.34 (1H, d, J=8.6 Hz).

(5) 3-(Aminomethyl)-6-chloro-4-isopropoxy-2-methyl-
5 1(2H)-isoquinolinone hydrochloride (synthesized
according to the method similar to that in Example 4
(7))

Melting point 218-220°C.

Elemental analysis for C₁₄H₁₈N₂O₂Cl₂ 1/2H₂O

10 Calculated: C, 52.27; H, 5.80; N, 8.71.

Found: C, 52.37; H, 5.84; N, 8.70.

¹H-NMR(DMSO-d₆) δ: 1.34 (6H, d, J=5.8 Hz), 3.61 (3H, s), 4.21-4.30 (3H, m), 7.65 (1H, dd, J=1.8, 8.6 Hz), 7.72 (1H, d, J=1.8 Hz), 8.28 (1H, d, J=8.6 Hz), 8.73 (3H, bs).

15 Example 7

3-(Aminomethyl)-4-butoxy-6-chloro-2-methyl-1(2H)-isoquinolinone hydrochloride

(1) Ethyl 4-butoxy-6-chloro-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the
20 method similar to that in Example 4 (2))

¹H-NMR(CDCl₃) δ: 1.01 (3H, t, J=7.3 Hz), 1.45 (3H, t, J=7.2 Hz), 1.51-1.63 (2H, m), 1.73-1.87 (2H, m), 3.52 (3H, s), 3.97 (2H, t, J=6.4 Hz), 4.48 (2H, q, J=7.2 Hz), 7.50 (1H, dd, J=2.0, 8.6 Hz), 7.71 (1H, d, J=2.0 Hz),
25 8.38 (1H, d, J=8.6 Hz).

(2) 4-Butoxy-6-chloro-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))
Melting point 160-161°C.

30 Elemental analysis for C₁₅H₁₆NO₄Cl

Calculated: C, 58.16; H, 5.21; N, 4.52.

Found: C, 58.34; H, 5.42; N, 4.58.

¹H-NMR(CDCl₃) δ: 0.95 (3H, t, J=7.2 Hz), 1.39-1.57 (2H, m), 1.67-1.80 (2H, m), 3.43 (3H, s), 3.95 (2H, t, J=6.4 Hz),
35 7.65 (1H, dd, J=2.0, 8.6 Hz), 7.73 (1H, d, J=2.0 Hz), 8.26 (1H, d, J=8.6 Hz).

(3) 4-Butoxy-6-chloro-3-hydroxymethyl-2-methyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))
Melting point 110-111°C.

⁵ Elemental analysis for C₁₅H₁₈NO₃Cl

Calculated: C, 60.91; H, 6.18; N, 4.74.

Found: C, 61.06; H, 6.09; N, 4.92.

¹H-NMR(CDCl₃) δ: 1.03 (3H, t, J=7.3 Hz), 1.50-1.65 (2H, m), 1.76-1.90 (2H, m), 2.82 (1H, bs), 3.69 (3H, s); 3.82 (2H,

¹⁰ t, J=6.4 Hz), 4.79 (2H, d, J=5.4 Hz), 7.39 (1H, dd, J=2.1, 8.5 Hz), 7.54 (1H, d, J=2.1 Hz), 8.24 (1H, d, J=8.5 Hz).

(4) 4-Butoxy-6-chloro-3-chloromethyl-2-methyl-1(2H)-isoquinolinone (synthesized according to the method

¹⁵ similar to that in Example 4 (5))

¹H-NMR(CDCl₃) δ: 1.05 (3H, t, J=7.3 Hz), 1.56-1.71 (2H, m), 1.83-1.97 (2H, m), 3.73 (3H, s), 3.99 (2H, t, J=6.4 Hz), 4.80 (2H, s), 7.46 (1H, dd, J=2.2, 8.6 Hz), 7.71 (1H, d, J=2.2 Hz), 8.38 (1H, d, J=8.6 Hz).

²⁰ (5) 2-((4-Butoxy-6-chloro-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl)-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6)).

Melting point 200-201°C.

²⁵ Elemental analysis for C₂₃H₂₁N₂O₄Cl

Calculated: C, 65.02; H, 4.98; N, 6.59.

Found: C, 64.85; H, 5.07; N, 6.60.

¹H-NMR(DMSO-d₆) δ: 0.93 (3H, t, J=7.4 Hz), 1.40-1.51 (2H, m), 1.70-1.81 (2H, m), 3.52 (3H, s), 3.93 (2H, t, J=6.6

³⁰ Hz), 5.03 (2H, s), 7.59 (1H, dd, J=2.0, 8.4 Hz), 7.67 (1H, d, J=2.0 Hz), 7.87 (4H, s), 8.25 (1H, d, J=8.4 Hz).

(6) 3-(Aminomethyl)-4-butoxy-6-chloro-2-methyl-1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 4 (7))

³⁵ Melting point 222-223°C.

Elemental analysis for C₁₅H₂₀N₂O₂Cl₂ 1/2H₂O

Calculated: C, 60.91; H, 6.13; N, 4.74.

Found: C, 61.06; H, 6.09; N, 4.92.

¹H-NMR(DMSO-d₆) δ:1.00 (3H, t, J=7.3 Hz), 1.46-1.64 (2H, m), 1.77-1.99 (2H, m), 3.61 (3H, s), 3.91 (2H, t, J=6.4 Hz), 4.23 (2H, bs), 7.65 (1H, dd, J=2.0, 8.6 Hz), 7.72 (1H, d, J=2.0 Hz), 8.28 (1H, d, J=8.6 Hz), 8.74 (3H, bs).

Example 8

3-(Aminomethyl)-4-benzyloxy-6-chloro-2-methyl-1(2H)-isoquinolinone hydrochloride

(1) Ethyl 4-benzyloxy-6-chloro-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 4 (2))

Melting point 114-115°C.

Elemental analysis for C₂₀H₁₈NO₄Cl

Calculated: C, 64.61; H, 4.88; N, 3.77.

Found: C, 64.67; H, 5.04; N, 4.00.

¹H-NMR(CDCl₃) δ:1.35 (3H, t, J=7.2 Hz); 3.54 (3H, s), 3.97 (2H, q, J=7.2 Hz), 5.03 (2H, s), 7.39-7.54 (6H, m), 7.72 (1H, d, J=1.8 Hz), 8.39 (1H, d, J=8.8 Hz).

(2) 4-Benzylxy-6-chloro-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))

Melting point 226-227°C.

Elemental analysis for C₁₈H₁₄NO₄Cl

Calculated: C, 62.89; H, 4.10; N, 4.07.

Found: C, 62.84; H, 4.16; N, 4.20.

¹H-NMR(CDCl₃) δ: 3.61 (3H, s), 5.07 (2H, s), 6.36 (1H, bs), 7.32-7.54 (6H, m), 7.72 (1H, d, J=1.8Hz), 8.37 (1H, d, J=8.4 Hz).

(3) 4-Benzylxy-6-chloro-3-hydroxymethyl-2-methyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))

Melting point 207-208°C.

Elemental analysis for C₁₈H₁₆NO₃Cl

Calculated: C, 65.56; H, 4.89; N, 4.25.

Found: C, 65.48; H, 4.96; N, 4.39.

¹H-NMR(CDCl₃) δ: 1.22 (1H, t, J=5.8Hz), 3.64 (3H, s), 4.52 (2H, d, J=5.8Hz), 4.96 (2H, s), 7.35-7.48 (6H, m), 7.72 (1H, d, J=2.2 Hz), 8.36 (1H, d, J=8.4 Hz).

⁵ (4) 4-Benzylxylo-6-chloro-3-chloromethyl-2-methyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

¹H-NMR(CDCl₃) δ: 3.74 (3H, s), 4.76 (2H, s), 5.04 (2H, s), 7.43-7.52 (6H, m), 7.75 (1H, d, J=2.2Hz), 8.40 (1H, d, J=8.8 Hz).

¹⁰ (5) 2-(4-Benzylxylo-6-chloro-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl)-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

Melting point 243-244°C.

¹⁵ Elemental analysis for C₂₆H₁₉N₂O₄Cl H₂O

Calculated: C, 65.48; H, 4.44; N, 5.87.

Found: C, 65.27; H, 4.22; N, 5.99..

¹H-NMR(DMSO-d₆) δ: 3.48 (3H, s), 5.06 (4H, s), 7.38-7.64 (7H, m), 7.85 (4H, s), 8.25 (1H, d, J=8.6 Hz).

²⁰ (6) 3-(Aminomethyl)-4-benzylxylo-6-chloro-2-methyl-1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 4 (7))

Melting point 221-223°C.

Elemental analysis for C₁₈H₁₈N₂O₂Cl₂ 1/2H₂O

²⁵ Calculated: C, 52.95; H, 6.22; N, 8.23.

Found: C, 53.21; H, 6.25; N, 8.28.

¹H-NMR(DMSO-d₆) δ: 3.62 (3H, s), 4.25 (2H, s), 5.02 (2H, s), 7.42-7.52 (7H, m), 7.59-7.69 (4H, m), 8.29 (1H, d, J=8.4 Hz), 8.72 (3H, bs).

³⁰ Example 9

3-(Aminomethyl)-6-chloro-2-methyl-4-(2-quinolinylmethoxy)-1(2H)-isoquinolinone hydrochloride

(1) Ethyl 6-chloro-2-methyl-1-oxo-4-(2-quinolinylmethoxy)-1,2-dihydro-3-isooquinolinecarboxylate

³⁵ (synthesized according to the method similar to that in Example 4 (2))

Melting point 164-165°C.

Elemental analysis for C₂₃H₁₉N₂O₄Cl

Calculated: C, 65.33; H, 4.53; N, 6.62.

Found: C, 65.29; H, 4.52; N, 6.33.

5 ¹H-NMR(CDCl₃) δ: 1.31 (3H, t, J=7.1 Hz), 3.56 (3H, s),
4.39 (2H, q, J=7.1 Hz), 5.33 (2H, s), 7.52 (1H, dd,
J=1.9, 8.6 Hz), 7.55-7.63 (1H, m), 7.72-7.82 (2H, m),
7.88 (1H, d, J=8.4 Hz), 7.93 (1H, d, J=1.9 Hz), 8.11 (1H,
d, J=8.6 Hz), 8.29 (1H, d, J=8.4 Hz), 8.41 (1H, d, J=8.4
10 Hz).

(2) 6-Chloro-2-methyl-1-oxo-4-(2-quinolinylmethoxy)-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))

15 Melting point 268-268°C.

¹H-NMR(DMSO-d₆) δ: 3.51 (3H, s), 5.29 (2H, s), 7.43 (1H, dd, J=2.0, 8.8 Hz), 7.59-7.67 (1H, m), 7.75-7.84 (2H, m), 7.87 (1H, d, J=8.6 Hz), 8.00-8.06 (2H, m), 8.19 (1H, d, J=8.6 Hz), 8.46 (1H, d, J=8.8 Hz).

20 (3) 6-Chloro-3-hydroxymethyl-2-methyl-4-(2-quinolinylmethoxy)-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))

Melting point 206-207°C.

25 Elemental analysis for C₂₁H₁₇N₂O₃Cl 1/4H₂O

Calculated: C, 65.46; H, 4.58; N, 7.27.

Found: C, 65.40; H, 4.47; N, 7.23.

¹H-NMR(CDCl₃) δ: 3.78 (3H, s), 4.80 (2H, s), 5.27 (2H, s), 7.42 (1H, dd, J=2.0, 8.6 Hz), 7.57-7.93 (5H, m), 8.12

30 (1H, d, J=8.8 Hz), 8.30 (1H, d, J=8.6 Hz), 8.36 (1H, d, J=8.8 Hz).

(4) 6-Chloro-3-chloromethyl-2-methyl-4-(2-quinolinylmethoxy)-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4

35 (5))

¹H-NMR(CDCl₃) δ: 3.76 (3H, s), 4.89 (2H, s), 5.33 (2H, s),

7.50 (1H, dd, J=2.0, 8.4 Hz), 7.57-7.65 (1H, m), 7.74-
 7.92 (3H, m), 7.95 (1H, d, J=2.0 Hz), 8.16 (1H, d,
 J=8.4 Hz), 8.31 (1H, d, J=8.4 Hz), 8.41 (1H, d, J=8.4 Hz).
 (5) 2-{(6-Chloro-2-methyl-1-oxo-4-(2-quinolinylmethoxy)-
 5 1,2-dihydro-3-isoquinolinyl)methyl}-1H-isoindole-
 1,3(2H)-dione (synthesized according to the method
 similar to that in Example 4 (6))
 Melting point 249-250°C.
¹H-NMR(DMSO-d₆) δ:3.53 (3H, s), 5.16 (2H, s), 5.30 (2H,
 10 s), 7.59-7.67 (2H, m), 7.80-7.83 (6H, m), 8.00-8.08 (3H,
 m), 8.27 (1H, d, J=9.0 Hz), 8.46 (1H, d, J=8.4 Hz).
 (6) 3-(Aminomethyl)-6-chloro-2-methyl-4-(2-
 quinolinylmethoxy)-1(2H)-isoquinolinone dihydrochloride
 (synthesized according to the method similar to that in
 15 Example 4 (7))
 Melting point 236°C..
 Elemental analysis for C₂₁H₂₀N₃O₂Cl₃ 1/4H₂O:
 Calculated: C, 55.16; H, 4.52; N, 9.19.
 Found: C, 55.29; H, 4.54; N, 9.12.
 20 ¹H-NMR(DMSO-d₆) δ:3.65 (3H, s), 4.41 (2H, d, J=4.8 Hz),
 5.44 (2H, s), 7.67 (1H, dd; J=2.0, 8.8 Hz), 7.17 (1H, t,
 J=7.3 Hz), 7.96 (1H, t, J=7.3 Hz), 8.07 (1H, d, J=8.6
 Hz), 8.15-8.20 (2H, m), 8.30 (1H, d, J=8.8 Hz), 8.33 (1H,
 d, J=8.4 Hz), 8.75 (1H, d, J=8.4 Hz), 8.87 (3H, bs).
 25 Example 10
 3-(Aminomethyl)-6-chloro-2-methyl-4-(2-phenylethoxy)-
 1(2H)-isoquinolinone hydrochloride
 (1) Ethyl 6-chloro-2-methyl-1-oxo-4-(2-phenylethoxy)-
 1,2-dihydro-3-isoquinolinecarboxylate (synthesized
 30 according to the method similar to that in Example 1
 (2))
¹H-NMR(CDCl₃) δ:1.38 (3H, t, J=7.2 Hz), 3.09 (2H, t,
 J=6.4 Hz), 3.49 (3H, s), 4.17 (2H, t, J=6.4 Hz), 4.33
 (2H, q, J=7.2 Hz), 7.24-7.40 (6H, m), 7.44 (1H, dd,
 35 J=2.1, 8.5 Hz), 8.33 (1H, d, J=8.5 Hz).
 (2) 6-Chloro-2-methyl-1-oxo-4-(2-phenylethoxy)-1,2-

dihydro-3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))

Melting point 168-169°C.

5 Elemental analysis for $C_{19}H_{16}NO_4Cl$

Calculated: C, 63.78; H, 4.51; N, 3.91.

Found: C, 63.73; H, 4.56; N, 3.86.

1H -NMR(DMSO-d₆) δ : 3.06 (2H, t, J=6.4 Hz), 3.43 (3H, s), 4.16 (2H, t, J=6.4 Hz), 7.19 (1H, dd, J=2.0 Hz), 7.28-

10 7.36 (5H, m), 7.58 (1H, dd, J=2.0, 8.6 Hz), 8.20 (1H, d, J=8.6 Hz).

(3) 6-Chloro-3-hydroxymethyl-2-methyl-4-(2-

phenylethoxy)-1(2H)-isoquinolinone (synthesized

according to the method similar to that in Example 4

15 (4))

Melting point 170-171°C.

Elemental analysis for $C_{19}H_{18}NO_3Cl$

Calculated: C, 66.38; H, 5.28; N, 4.07.

Found: C, 66.18; H, 5.20; N, 3.93.

20 1H -NMR(CDCl₃) δ : 2.08 (1H, bs), 3.14 (2H, t, J=6.2 Hz), 3.67 (3H, s), 4.08 (2H, t, J=6.2 Hz), 4.59 (2H, d, J=5.8 Hz), 7.26-7.43 (7H, m), 8.27 (1H, d, J=8.4 Hz).

(4) 6-Chloro-3-chloromethyl-2-methyl-4-(2-phenylethoxy)-1(2H)-isoquinolinone (synthesized according to the

25 method similar to that in Example 4 (5))

1H -NMR(CDCl₃) δ : 3.19 (2H, t, J=6.4 Hz), 3.69 (3H, s), 4.20 (2H, t, J=6.4 Hz), 4.58 (2H, s), 7.34-7.42 (6H, m), 7.46 (1H, d, J=2.2 Hz), 8.34 (1H, d, J=8.0 Hz).

(5) 2-((6-Chloro-2-methyl-1-oxo-4-(2-phenylethoxy)-1,2-dihydro-3-isoquinolinyl)methyl)-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

Melting point 219-220°C.

Elemental analysis for $C_{27}H_{21}N_2O_4Cl$

35 Calculated: C, 68.57; H, 4.48; N, 5.92.

Found: C, 68.29; H, 4.54; N, 5.97.

¹H-NMR(DMSO-d₆) δ:3.06 (2H, t, J=6.4 Hz), 3.49 (3H, s), 4.14 (2H, t, J=6.4 Hz), 4.96 (2H, s), 7.19-7.30 (6H, m), 7.52 (1H, dd, J=2.2, 8.6 Hz), 7.89 (4H, s), 8.19 (1H, d, J=8.6 Hz).

⁵ (6) Tert-butyl (6-chloro-2-methyl-1-oxo-4-(2-phenylethoxy)-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 1 (6))
Melting point 163-164°C.

¹⁰ Elemental analysis for C₂₄H₂₇N₂O₄Cl

Calculated: C, 65.08; H, 6.14; N, 6.32.

Found: C, 65.16; H, 6.32; N, 6.15.

¹H-NMR(CDCl₃) δ:1.47 (9H, s), 3.15 (2H, t, J=6.4 Hz), 3.59 (3H, s), 4.04 (2H, t, J=6.4 Hz), 4.34 (2H, d, J=6.0

¹⁵ Hz), 4.60 (1H, bs), 7.27-7.41 (7H, m), 8.29 (1H, d, J=8.8 Hz).

(7) 3-(Aminomethyl)-6-chloro-2-methyl-4-(2-phenylethoxy)-1(2H)-isoquinolinone hydrochloride
(synthesized according to the method similar to that in

²⁰ Example 1 (7)).

Melting point 200-201°C.

Elemental analysis for C₁₉H₂₀N₂O₂Cl₂ 3/4H₂O

Calculated: C, 58.10; H, 5.52; N, 7.13..

Found: C, 58.23; H, 5.77; N, 7.11.

²⁵ ¹H-NMR(DMSO-d₆) δ:3.16 (2H, t, J=6.4 Hz), 3.58 (3H, s), 4.11 (2H, t, J=6.4 Hz), 4.25 (2H, d, J=5.6 Hz), 7.21 (1H, d, J=2.0 Hz), 7.29-7.45 (5H, m), 7.58 (1H, dd, J=2.0, 8.6 Hz), 8.22 (1H, d, J=8.6 Hz), 8.68 (3H, bs).

Example 11

³⁰ 3-(Aminomethyl)-6-chloro-2-methyl-4-(1-naphthylmethoxy)-1(2H)-isoquinolinone hydrochloride

(1) Ethyl 6-chloro-2-methyl-4-(1-naphthylmethoxy)-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1

³⁵ (2))

Melting point 158-159°C.

Elemental analysis for C₂₄H₂₀NO₄Cl

Calculated: C, 68.33; H, 4.78; N, 3.32.

Found: C, 68.25; H, 4.559; N, 3.21.

¹H-NMR(CDCl₃) δ:1.24 (3H, t, J=7.2 Hz), 3.53 (3H, s),

5 4.19 (2H, q, J=7.2 Hz), 5.50 (2H, s), 7.45-7.63 (5H, m),
7.68 (1H, d, J=2.2 Hz), 7.87-7.95 (2H, m), 8.09-8.14 (1H,
m), 8.39 (1H, d, J=8.4 Hz).

(2) 6-Chloro-2-methyl-4-(1-naphthylmethoxy)-1-oxo-1,2-dihydro-3-isouquinolinecarboxylic acid (synthesized

10 according to the method similar to that in Example 4
(3))

Melting point 166-167°C.

Elemental analysis for C₂₂H₁₆NO₄Cl

Calculated: C, 67.10; H, 4.10; N, 3.56.

15 Found: C, 66.93; H, 3.95; N, 3.49.
¹H-NMR(DMSO-d₆) δ:3.50 (3H, s), 5.49 (2H, s), 7.51-7.68
(6H, m), 7.96-8.04 (2H, m), 8.20-8.28 (2H, m).

(3) 6-Chloro-3-hydroxymethyl-2-methyl-4-(1-naphthylmethoxy)-1(2H)-isouquinolinone (synthesized
20 according to the method similar to that in Example 4..
(4))

Melting point 202-203°C.

Elemental analysis for C₂₂H₁₈NO₃Cl

Calculated: C, 69.57; H, 4.78; N, 3.69.

25 Found: C, 69.18; H, 5.11; N, 3.61.
¹H-NMR(DMSO-d₆) δ:3.64 (3H, s), 4.63 (2H, d, J=5.0 Hz),
5.47 (2H, s), 5.59 (1H, t, J=5.0 Hz), 7.50-7.69 (6H, m),
7.96-8.04 (2H, m), 8.21-8.25 (2H, m).

(4) 6-Chloro-3-chloromethyl-2-methyl-4-(1-naphthylmethoxy)-1(2H)-isouquinolinone (synthesized
30 according to the method similar to that in Example 4
(5))

¹H-NMR(CDCl₃) δ:3.72 (3H, s), 4.67 (2H, s), 5.52 (2H, s),
7.45-7.67 (6H, m), 7.71 (1H, d, J=1.8 Hz), 7.89-7.97 (2H,
m), 8.16 (1H, d, J=8.0 Hz), 8.39 (1H, d, J=8.4 Hz).
(5) 2-{(6-Chloro-2-methyl-4-(1-naphthylmethoxy)-1-oxo-

1,2-dihydro-3-isoquinolinyl)methyl}-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))
Melting point 211-212°C.

⁵ ¹H-NMR(DMSO-d₆) δ: 3.49 (3H, s), 5.09 (2H, s), 5.58 (2H, s), 7.45-7.68 (6H, m), 7.84 (4H, s), 7.91-8.01 (2H, m), 8.14-8.19 (1H, m), 8.23 (1H, d, J=8.8 Hz).

(6) Tert-butyl (6-chloro-2-methyl-4-(1-naphthylmethoxy)-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate

¹⁰ (synthesized according to the method similar to that in Example 1 (6))

Melting point 205-206°C.

Elemental analysis for C₂₇H₂₇N₂O₄Cl

Calculated: C, 67.71; H, 5.68; N, 5.85.

¹⁵ Found: C, 67.50; H, 5.90; N, 5.70.

¹H-NMR(CDCl₃) δ: 1.37 (9H, s), 3.14 (1H, bs), 3.45 (3H, s), 4.02 (2H, d, J=6.2 Hz), 5.44 (2H, s), 7.29 (1H, d, J=7.2 Hz), 7.41-7.51 (2H, m), 7.72 (1H, d, J=2.0 Hz), 7.55-7.69 (2H, m), 7.81 (1H, d, J=1.8 Hz), 7.91-7.95 (2H, m),

²⁰ 8.24 (1H, d, J=8.2 Hz), 8.39 (1H, d, J=8.8 Hz).

(7) 3-(Aminomethyl)-6-chloro-2-methyl-4-(1-naphthylmethoxy)-1(2H)-isoquinolinone hydrochloride

(synthesized according to the method similar to that in Example 1 (7))

²⁵ Melting point 226-227°C.

Elemental analysis for C₂₂H₂₀N₂O₂Cl₂ 1/4H₂O

Calculated: C, 62.94; H, 4.92; N, 6.67.

Found: C, 63.01; H, 4.79; N, 6.59.

¹H-NMR(DMSO-d₆) δ: 3.65 (3H, s), 4.29 (2H, d, J=4.2 Hz),

³⁰ 5.55 (2H, s), 7.52-7.78 (6H, m), 7.98-8.06 (2H, m),

8.22-8.30 (2H, m), 8.81 (3H, bs).

Example 12

3-(Aminomethyl)-7-chloro-2-methyl-4-phenyl-1(2H)-isoquinolinone hydrochloride

³⁵ (1) To a solution of ethyl 7-chloro-4-hydroxy-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized

according to the method similar to that in Example 5
(1)) (2.82 g, 10 mmol) in tetrahydrofuran (20 ml) was added sodium hydride (0.48 g, 12 mmol)(60% in oil) at 0°C and the mixture was stirred at 0°C for 30 min. To 5 the obtained mixture was added N-phenyltrifluoromethane sulfonimide (4.29 g, 12 mmol) and the mixture was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the 10 extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give ethyl 7-chloro-2-methyl-1-oxo-4-trifluoromethane-sulfonyloxy-1,2-dihydro-3-isoquinolinecarboxylate (2.95 15 g, 71.4%) as an oil.

¹H-NMR(CDCl₃) δ:1.45 (3H, d, J=7.2 Hz), 3.61 (3H, s), 4.49 (2H, q, J=7.2 Hz), 7.75-7.76 (2H, m), 8.44-8.45 (1H, m).

(2) A mixture of ethyl 7-chloro-2-methyl-1-oxo-4-trifluoromethanesulfonyloxy-1,2-dihydro-3-isoquinolinecarboxylate (2.90 g, 7 mmol), phenylboronic acid (1.02 g, 8.4 mmol) and sodium carbonate (1.85 g, 17.5 mmol) in toluene (20 ml), ethanol (4 ml) and water (4 ml) was stirred under an argon atmosphere at room 25 temperature for 30 min. To the obtained mixture was added tetrakis(triphenylphosphine)palladium (0.46 g, 4 mmol) and the mixture was refluxed under heating under an argon atmosphere for 12 h. The reaction mixture was poured into water and extracted with ethyl acetate. 30 After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give ethyl 7-chloro-2-methyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinecarboxylate (1.70 g, 71.1%) as crystals. 35 Melting point 152-153°C.

¹H-NMR(CDCl₃) δ: 0.92 (3H, t, J=7.1 Hz), 3.62 (3H, s), 4.02 (2H, q, J=7.1 Hz), 7.17 (1H, dd, J=8.8 Hz), 7.28-7.33 (2H, m), 7.41-7.53 (4H, m), 8.48 (1H, d, J=2.2 Hz).

- (3) 7-Chloro-2-methyl-1-oxo-4-phenyl-1,2-dihydro-3-
⁵ isoquinolinecarboxylic acid (synthesized according to
the method similar to that in Example 4 (3))
Melting point 261-262°C.

¹H-NMR(CDCl₃) δ: 3.68 (3H, s), 7.13 (1H, d, J=8.8 Hz), 7.32-7.51 (6H, m), 8.45 (1H, d, J=2.2 Hz).

- (4) 7-Chloro-3-hydroxymethyl-2-methyl-4-phenyl-1(2H)-
isoquinolinone (synthesized according to the method
similar to that in Example 4 (4))
Melting point 199-200°C.

Elemental analysis for C₁₇H₁₄NO₂Cl

- ¹⁵ Calculated: C, 68.12; H, 4.71; N, 4.67.

Found: C, 68.25; H, 4.71; N, 4.49.

¹H-NMR(CDCl₃) δ: 2.17 (1H, t, J=5.5 Hz), 3.82 (3H, s), 4.40 (2H, d, J=5.5 Hz), 6.96 (1H, d, J=8.8 Hz), 7.26-7.33 (2H, m), 7.39 (1H, dd, J=2.2, 8.8 Hz), 7.45-7.54

- ²⁰ (3H, m), 8.39 (1H, d, J=2.2 Hz).

(5) 7-Chloro-3-chloromethyl-2-methyl-4-phenyl-1(2H)-
isoquinolinone (synthesized according to the method
similar to that in Example 4 (5))

¹H-NMR(CDCl₃) δ: 3.84 (3H, s), 4.40 (2H, s), 6.99 (1H, d,

- ²⁵ J=8.4 Hz), 7.31-7.35 (2H, m), 7.42-7.56 (4H, m), 8.47 (1H, d, J=2.2 Hz).

(6) 2-((7-Chloro-2-methyl-1-oxo-4-phenyl-1,2-dihydro-3-
isoquinolinyl)methyl)-1H-isoindole-1,3(2H)-dione.

- (synthesized according to the method similar to that in
³⁰ Example 4 (6))

Melting point 241-242°C.

Elemental analysis for C₂₅H₁₇N₂O₃Cl

Calculated: C, 70.01; H, 4.00; N, 6.53.

Found: C, 69.69; H, 4.13; N, 6.56.

- ³⁵ ¹H-NMR(DMSO-d₆) δ: 3.61 (3H, s), 4.76 (2H, s), 6.89 (1H, d, J=8.8 Hz), 7.26-7.31 (2H, m), 7.40-7.43 (3H, m), 7.66

(1H, dd, J=2.2, 8.8 Hz), 7.74-7.83 (4H, m), 8.23 (1H, d, J=2.2 Hz).

(7) 3-(Aminomethyl)-7-chloro-2-methyl-4-phenyl-1(2H)-isoquinolinone hydrochloride (synthesized according to

⁵ the method similar to that in Example 4 (7))

Melting point 242-243°C.

Elemental analysis for C₁₇H₁₆N₂OCl₂ 1/2H₂O

Calculated: C, 59.31; H, 4.98; N, 8.14.

Found: C, 59.50; H, 4.97; N, 8.14.

¹⁰ ¹H-NMR(DMSO-d₆) δ:3.72 (3H, s), 3.93 (2H, s), 6.94 (1H, d, J=8.6 Hz), 7.37-7.41 (2H, m), 7.56-7.59 (3H, m), 7.72 (1H, dd, J=2.4, 8.6 Hz), 8.27 (1H, d, J=2.4 Hz), 8.65 (3H, bs).

Example 13

¹⁵ 3-(Aminomethyl)-6-chloro-2-methyl-4-propoxy-1(2H)-isoquinolinone hydrochloride

(1) Ethyl 6-chloro-2-methyl-4-propoxy-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (2))

²⁰ ¹H-NMR(CDCl₃) δ:1.08 (3H, t, J=7.3 Hz), 1.45 (3H, t, J=7.2 Hz); 1.76-1.89 (2H, m), 3.51 (3H, s), 3.93 (2H, t, J=6.6 Hz), 4.48 (2H, q, J=7.2 Hz), 7.49 (1H, dd, J=2.0, 8.6 Hz), 7.71 (1H, d, J=2.0 Hz), 8.37 (1H, d, J=8.6 Hz).

(2) 6-Chloro-2-methyl-1-oxo-4-propoxy-1,2-dihydro-3-

²⁵ isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))

Melting point 164-165°C.

Elemental analysis for C₁₄H₁₄NO₄Cl

Calculated: C, 56.86; H, 4.77; N, 4.74.

³⁰ Found: C, 56.82; H, 4.70; N, 4.52.

¹H-NMR(CDCl₃) δ:1.08 (3H, t, J=7.3 Hz), 1.77-1.95 (2H, m), 3.65 (3H, s), 3.97 (2H, t, J=6.6 Hz), 7.51 (1H, dd, J=2.0, 8.6 Hz), 7.64 (1H, d, J=2.0 Hz), 7.67 (1H, bs), 8.31 (1H, d, J=8.6 Hz).

³⁵ (3) 6-Chloro-3-hydroxymethyl-2-methyl-4-propoxy-1(2H)-isoquinolinone (synthesized according to the method

similar to that in Example 4 (4))

Melting point 95.5-96.5°C.

Elemental analysis for C₁₄H₁₅NO₃Cl

Calculated: C, 59.68; H, 5.72; N, 4.97.

⁵ Found: C, 59.38; H, 5.69; N, 4.87.

¹H-NMR(CDCl₃) δ: 1.14 (3H, t, J=7.3 Hz), 1.79-1.93 (2H, m), 2.89 (1H, bs), 3.69 (3H, s), 3.79 (2H, t, J=6.6 Hz), 4.79 (2H, d, J=4.8 Hz), 7.39 (1H, dd, J=2.0, 8.6 Hz), 7.55 (1H, d, J=2.0 Hz), 8.24 (1H, dd, J=3.8, 8.6 Hz).

¹⁰ (4) 6-Chloro-3-chloromethyl-2-methyl-4-propoxy-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

¹H-NMR(CDCl₃) δ: 1.16 (3H, t, J=7.3 Hz), 1.86-2.00 (2H, m), 3.73 (3H, s), 3.95 (2H, t, J=6.6 Hz), 4.80 (2H, s), 7.48

¹⁵ (1H, dd, J=2.0, 8.6 Hz), 7.71 (1H, d, J=2.0 Hz), 8.38 (1H, d, J=8.6 Hz).

(5) 2-((6-Chloro-2-methyl-4-propoxy-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl)-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in

²⁰ Example 4 (6))

Melting point 193-194°C.

Elemental analysis for C₂₂H₁₉N₂O₄Cl

Calculated: C, 64.31; H, 4.66; N, 6.82.

Found: C, 63.96; H, 4.51; N, 6.48.

²⁵ ¹H-NMR(DMSO-d₆) δ: 1.00 (3H, t, J=7.4 Hz), 1.72-1.86 (2H, m), 3.51 (3H, s), 3.90 (2H, t, J=6.7 Hz), 5.03 (2H, s), 7.59 (1H, dd, J=1.8, 8.4 Hz), 7.68 (1H, d, J=1.8 Hz), 7.86 (4H, s), 8.24 (1H, d, J=8.4 Hz).

³⁰ (6) Tert-butyl (6-chloro-2-methyl-4-propoxy-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 1 (6))

Melting point 104-105°C.

Elemental analysis for C₁₉H₂₅N₂O₄Cl

³⁵ Calculated: C, 59.92; H, 6.62; N, 7.36.

Found: C, 59.87; H, 6.34; N, 7.23.

¹H-NMR(CDCl₃) δ: 1.13 (3H, t, J=7.4 Hz), 1.47 (9H, s), 1.85-1.96 (2H, m), 3.62 (3H, s), 3.80 (2H, t, J=6.6 Hz), 4.53 (2H, d, J=6.0 Hz), 4.77 (1H, bs), 7.43 (1H, dd, J=2.0, 8.6 Hz), 7.65 (1H, d, J=2.0 Hz), 8.33 (1H, d, ⁵J=8.6 Hz).

(7) 3-(Aminomethyl)-6-chloro-2-methyl-4-propoxy-1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7)) Melting point 226-227°C.

¹⁰ Elemental analysis for C₁₄H₁₈N₂O₂Cl₂ 1/2H₂O

Calculated: C, 51.55; H, 5.87; N, 8.59.

Found: C, 51.61; H, 6.13; N, 8.44.

¹H-NMR(DMSO-d₆) δ: 1.09 (3H, t, J=7.4 Hz), 1.79-1.93 (2H, m), 3.39 (3H, s), 3.88 (2H, t, J=6.4 Hz), 4.24 (2H, s), ¹⁵ 7.66 (1H, dd, J=2.0, 8.6 Hz), 7.74 (1H, d, J=2.0 Hz), 8.28 (1H, d, J=8.6 Hz), 8.78 (3H, bs).

Example 14

3-(Aminomethyl)-6-chloro-4-cyclopentylmethoxy-2-methyl-1(2H)-isoquinolinone hydrochloride

²⁰ (1) Ethyl 6-chloro-4-cyclopentylmethoxy-2-methyl-1-oxo-1,2-dihydro-3-isooquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (2))

Melting point 89-90°C.

²⁵ Elemental analysis for C₁₉H₂₂NO₄Cl 1/4H₂O

Calculated: C, 61.96; H, 6.15; N, 3.80.

Found: C, 61.91; H, 6.03; N, 3.93.

¹H-NMR(CDCl₃) δ: 1.33-1.43 (2H, m), 1.45 (3H, t, J=7.2 Hz), 1.61-1.72 (4H, m), 1.89-1.93 (2H, m), 2.32-2.47 (1H, m), ³⁰ 3.51 (3H, s), 3.85 (2H, d, J=6.8 Hz), 4.47 (2H, q, J=7.2 Hz), 7.50 (1H, dd, J=2.0, 8.6 Hz), 7.72 (1H, d, J=2.0 Hz), 8.37 (1H, d, J=8.6 Hz).

(2) 6-Chloro-4-cyclopentylmethoxy-2-methyl-1-oxo-1,2-dihydro-3-isooquinolinecarboxylic acid (synthesized

³⁵ according to the method similar to that in Example 4 (3))

Melting point 191-192°C.

Elemental analysis for C₁₇H₁₈NO₄Cl 1/4H₂O

Calculated: C, 60.00; H, 5.48; N, 4.12.

Found: C, 60.20; H, 5.28; N, 4.09.

⁵ ¹H-NMR(DMSO-d₆) δ:1.33-1.46 (2H, m), 1.58-1.60 (4H, m), 1.71-1.86 (2H, m), 2.30-2.45 (1H, m), 3.43 (3H, s), 3.82 (2H, d, J=6.8 Hz), 7.65 (1H, dd, J=2.0, 8.6 Hz), 7.71 (1H, d, J=2.0 Hz), 8.26 (1H, d, J=8.6 Hz)

¹⁰ (3) 6-Chloro-4-cyclopentylmethoxy-3-hydroxymethyl-2-methyl-1(2H)-isoquinolinone (*synthesized according to the method similar to that in Example 4 (4)*).

Melting point 127-128°C.

Elemental analysis for C₁₇H₂₀NO₃Cl 1/4H₂O

Calculated: C, 62.57; H, 6.33; N, 4.29.

¹⁵ Found: C, 62.61; H, 6.21; N, 4.23.
¹H-NMR(CDCl₃) δ:1.35-1.51 (2H, m), 1.61-1.74 (4H, m), 1.84-1.97 (2H, m), 2.36-2.51 (1H, m), 3.71 (5H, s), 4.81 (2H, d, J=5.0 Hz), 7.40 (1H, dd, J=2.0, 8.6 Hz), 7.60 (1H, d, J=2.0 Hz), 8.28 (1H, d, J=8.6 Hz).

²⁰ (4) 6-Chloro-3-chloromethyl-4-cyclopentylmethoxy-2-methyl-1(2H)-isoquinolinone (*synthesized according to the method similar to that in Example 4 (5)*).

¹H-NMR(CDCl₃) δ:1.36-1.71 (6H, m), 1.85-1.97 (2H, m), 2.37-2.57 (1H, m), 3.73 (3H, s), 3.87 (2H, d, J=7.0 Hz), 4.80 (2H, s), 7.48 (1H, dd, J=2.2, 8.8 Hz), 7.72 (1H, d, J=2.2 Hz), 8.37 (1H, d, J=8.8 Hz).

(5) 2-((6-Chloro-4-cyclopentylmethoxy-2-methyl-1-oxo-1,2-dihydro-3-isooquinolinyl)methyl)-1H-isooindole-1,3(2H)-dione (*synthesized according to the method similar to that in Example 4 (6)*).

Melting point 204-205°C.

Elemental analysis for C₂₅H₂₃N₂O₄Cl 3/4H₂O

Calculated: C, 64.65; H, 5.32; N, 6.03.

Found: C, 64.85; H, 5.08; N, 6.09.

³⁵ ¹H-NMR(DMSO-d₆) δ:1.23-1.63 (6H, m), 1.72-1.84 (2H, m), 2.33-2.46 (1H, m), 3.48 (3H, s), 3.83 (2H, d, J=6.8 Hz),

7.59 (1H, dd, J=2.0, 8.6 Hz), 7.68 (1H, d, J=2.0 Hz),
7.82-7.91 (4H, m), 8.37 (1H, d, J=8.8 Hz).

(6) Tert-butyl (6-chloro-4-cyclopentylmethoxy-2-methyl-
1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate

⁵ (synthesized according to the method similar to that in
Example 1 (6))

Melting point 161-162°C.

Elemental analysis for C₂₂H₂₉N₂O₄Cl

Calculated: C, 62.77; H, 6.94; N, 6.66.

¹⁰ Found: C, 62.49; H, 7.15; N, 6.60.

¹H-NMR(CDCl₃) δ:1.26-1.44 (2H, m), 1.47 (9H, s), 1.60-
1.71 (4H, m), 1.87-1.99 (2H, m), 2.38-2.53 (1H, m), 3.62
(3H, s), 3.72 (2H, d, J=6.8 Hz), 4.53 (2H, d, J=5.8 Hz),
7.43 (1H, dd, J=1.8, 8.6 Hz), 7.66 (1H, d, J=1.8 Hz),
¹⁵ 8.33 (1H, d, J=8.6 Hz).

(7) 3-(Aminomethyl)-6-chloro-4-cyclopentylmethoxy-2-
methyl-1(2H)-isoquinolinone hydrochloride (synthesized
according to the method similar to that in Example 1
(7))

²⁰ Melting point 217-219°C.

Elemental analysis for C₁₇H₂₂N₂O₂Cl₂ 1/2H₂O

Calculated: C, 55.74; H, 6.33; N, 7.65.

Found: C, 55.75; H, 6.32; N, 7.69.

¹H-NMR(DMSO-d₆) δ:1.37-1.68 (6H, m), 1.81-1.93 (2H, m),
²⁵ 2.39-2.54 (1H, m), 3.61 (3H, s), 3.80 (2H, d, J=6.8 Hz),
4.24 (2H, d, J=5.2 Hz), 7.65 (1H, dd, J=2.0, 8.4 Hz),
7.72 (1H, d, J=2.0 Hz), 8.28 (1H, d, J=8.4 Hz), 8.77 (3H,
bs).

Example 15

³⁰ 3-(Aminomethyl)-6-chloro-2-methyl-4-(4-nitrophenoxy)-
1(2H)-isoquinolinone hydrochloride

(1) Ethyl 6-chloro-2-methyl-4-(4-nitrophenoxy)-1-oxo-
1,2-dihydro-3-isoquinolinecarboxylate (synthesized
according to the method similar to that in Example 4

³⁵ (2))

Melting point 184-185°C.

Elemental analysis for C₁₉H₁₅N₂O₆Cl 1/4H₂O

Calculated: C, 56.66; H, 3.75; N, 6.95.

Found: C, 56.70; H, 3.85; N, 6.81.

¹H-NMR(CDCl₃) δ: 1.12 (3H, t, J=7.2 Hz), 3.60 (3H, s),

5 4.28 (2H, q, J=7.2 Hz), 7.05 (2H, d, J=9.2 Hz), 7.35 (1H, d, J=2.0 Hz), 7.55 (1H, dd, J=2.0, 8.8 Hz), 8.24 (2H, d, J=9.2 Hz), 8.44 (1H, d, J=8.8 Hz).

(2) 6-Chloro-2-methyl-4-(4-nitrophenoxy)-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized

10 according to the method similar to that in Example 4 (3))

Melting point 240-241°C.

Elemental analysis for C₁₇H₁₁N₂O₆Cl 1/2AcOEt

Calculated: C, 54.49; H, 3.61; N, 6.69.

15 Found: C, 54.63; H, 3.64; N, 6.69.

¹H-NMR(CDCl₃) δ: 3.51 (3H, s), 7.28 (2H, d, J=9.2 Hz), 7.36 (1H, d, J=2.0 Hz), 7.68 (1H, d, J=2.0, 8.6 Hz), 8.22 (2H, d, J=9.2 Hz), 8.33 (1H, d, J=8.6 Hz).

(3) 6-Chloro-3-hydroxymethyl-2-methyl-4-(4-

20 nitrophenoxy)-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))

Melting point 249-250°C.

Elemental analysis for C₁₇H₁₃N₂O₅Cl

25 Calculated: C, 56.60; H, 3.63; N, 7.77.

Found: C, 56.68; H, 3.83; N, 7.65.

¹H-NMR(CDCl₃) δ: 3.80 (3H, s), 4.35 (1H, bs), 4.64 (2H, d, J=5.2 Hz), 7.07 (2H, d, J=9.1 Hz), 7.32 (1H, d, J=2.0 Hz), 7.47 (1H, dd, J=2.0, 8.6 Hz), 8.22 (2H, d, J=9.1 Hz), 8.40 (1H, d, J=8.6 Hz).

(4) 6-Chloro-3-chloromethyl-2-methyl-4-(4-nitrophenoxy)-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

¹H-NMR(CDCl₃) δ: 3.79 (3H, s), 4.65 (2H, s), 7.06 (2H, d,

35 J=9.1 Hz), 7.34 (1H, d, J=1.8 Hz), 7.52 (1H, dd, J=1.8, 8.8 Hz), 8.24 (2H, d, J=9.1 Hz), 8.44 (1H, d, J=8.8 Hz).

(5) 2-[(6-Chloro-2-methyl-4-(4-nitrophenoxy)-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl]-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

5 Melting point 257-258°C.

Elemental analysis for C₂₅H₁₆N₃O₆Cl

Calculated: C, 61.30; H, 3.29; N, 8.58.

Found: C, 61.10; H, 3.38; N, 8.41.

¹H-NMR(DMSO-d₆) δ:3.81 (3H, s), 4.94 (2H, s), 6.92 (2H, d, J=9.4 Hz), 7.24 (1H, d, J=1.8 Hz), 7.60-7.72 (5H, m), 7.88 (2H, d, J=9.4 Hz), 8.33 (1H, d, J=8.4 Hz).

(6) Tert-butyl [6-chloro-2-methyl-4-(4-nitrophenoxy)-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate
(synthesized according to the method similar to that in

15 Example 1 (6))

Melting point 198-199°C.

Elemental analysis for C₂₂H₂₂N₃O₆Cl

Calculated: C, 57.46; H, 4.82; N, 9.14.

Found: C, 57.44; H, 4.80; N, 9.25.

¹H-NMR(CDCl₃) δ:1.41 (9H, s), 3.70 (3H, s), 4.41 (2H, d, J=5.8 Hz), 4.64 (1H, bs), 7.03 (2H, d, J=9.4 Hz), 7.29 (1H, d, J=2.0 Hz), 7.48 (1H, d, J=2.0, 8.6 Hz), 8.24 (2H, d, J=9.4 Hz), 8.40 (1H, d, J=8.6 Hz).

(7) 3-(Aminomethyl)-6-chloro-2-methyl-4-(4-nitrophenoxy)-1(2H)-isoquinolinone hydrochloride
(synthesized according to the method similar to that in Example 1 (7))

Melting point 242-243°C.

Elemental analysis for C₁₇H₁₅N₃O₄Cl₂ 1/4H₂O

30 Calculated: C, 50.95; H, 3.90; N, 10.49.

Found: C, 51.05; H, 3.92; N, 10.23.

¹H-NMR(DMSO-d₆) δ:3.68 (3H, s), 4.08 (2H, bs), 7.35 (2H, d, J=9.4Hz), 7.38 (1H, d, J=2.0 Hz), 7.68 (1H, d, J=2.0, 8.6 Hz), 8.26 (2H, d, J=9.4Hz), 8.34 (1H, d, J=8.6 Hz), 8.83 (3H, bs).

Example 16

3-(Aminomethyl)-6-chloro-4-(4-methoxyphenyl)-2-methyl-1(2H)-isoquinolinone hydrochloride

(1) To a solution of ethyl 6-chloro-4-hydroxy-2-methyl-1-oxo-1,2-dihydro-3-isouquinolinecarboxylate (synthesized

5 according to the method similar to that in Example 5

(1)) (8.45 g, 30 mmol) in tetrahydrofuran (100 ml) was added sodium hydride (1.44 g, 36 mmol) (60% in oil) at 0°C and the mixture was stirred at 0°C for 30 min. To the obtained mixture was added N-phenyltrifluoromethane

10 sulfonimide (12.86 g, 36 mmol) and the mixture was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and

15 concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give ethyl 6-chloro-2-methyl-1-oxo-4-trifluoromethane-sulfonyloxy-1,2-dihydro-3-isouquinolinecarboxylate (8.54 g, 68.8%) as crystals.

20 $^1\text{H-NMR}(\text{CDCl}_3)$ δ : 1.45 (3H, t, J=7.0 Hz), 3.60 (3H, s), 4.49 (2H, q, J=7.0 Hz), 7.60 (1H, dd, J=2.0, 8.6 Hz), 7.75 (1H, d, J=2.0 Hz), 8.40 (1H, d, J=8.6 Hz).

(2) Ethyl 6-chloro-4-(4-methoxyphenyl)-2-methyl-1-oxo-1,2-dihydro-3-isouquinolinecarboxylate (synthesized

25 according to the method similar to that in Example 12 (2)).

Melting point 135-136°C.

Elemental analysis for $\text{C}_{20}\text{H}_{18}\text{NO}_4\text{Cl}$

Calculated: C, 64.61; H, 4.88; N, 3.77.

30 Found: C, 64.81; H, 4.87; N, 3.57.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ : 1.00 (3H, t, J=7.2 Hz), 3.59 (3H, s), 3.88 (3H, s), 4.07 (2H, q, J=7.2 Hz), 6.98 (2H, d, J=8.8 Hz), 7.232 (2H, d, J=8.8 Hz), 7.24 (1H, d, J=2.0 Hz), 7.47 (1H, d, J=2.0, 8.6 Hz), 8.34 (1H, d, J=8.6 Hz).

35 (3) 6-Chloro-4-(4-methoxyphenyl)-2-methyl-1-oxo-1,2-dihydro-3-isouquinolinecarboxylic acid (synthesized

according to the method similar to that in Example 4

(3))

Melting point 242-243°C.

Elemental analysis for C₁₈H₁₄NO₄Cl

⁵ Calculated: C, 62.89; H, 4.10; N, 4.07.

Found: C, 63.06; H, 4.18; N, 4.01.

¹H-NMR(CDCl₃) δ:3.52 (3H, s), 3.83 (3H, s), 7.04 (1H, d, J=2.2 Hz), 7.06 (2H, d, J=8.6 Hz), 7.26 (2H, d, J=8.6 Hz), 7.62 (1H, d, J=2.2, 8.6 Hz), 8.32 (1H, d, J=8.6 Hz).

¹⁰ (4) 6-Chloro-4-(4-methoxyphenyl)-3-hydroxymethyl-2-methyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))

Melting point 187-188°C.

Elemental analysis for C₁₈H₁₆NO₃Cl

¹⁵ Calculated: C, 65.56; H, 4.89; N, 4.25...

Found: C, 65.62; H, 5.04; N, 4.09.

¹H-NMR(CDCl₃) δ:2.26 (1H, bs), 3.80 (3H, s), 3.90 (3H, s), 4.47 (2H, d, J=5.6 Hz), 7.01-7.06 (3H, m), 7.18-7.25 (3H, m), 7.35 (1H, dd, J=1.8, 8.6 Hz), 8.33 (1H, d, J=8.6 Hz).

²⁰ (5) 6-Chloro-3-chloromethyl-4-(4-methoxyphenyl)-2-methyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

¹H-NMR(CDCl₃) δ:3.82 (3H, s), 3.91 (3H, s), 4.41 (2H, s),

²⁵ 7.03-7.08 (3H, m), 7.24 (2H, d, J=8.0 Hz), 7.43 (1H, dd, J=2.0, 8.6 Hz), 8.42 (1H, d, J=8.6 Hz).

(6) 2-{(6-Chloro-4-(4-methoxyphenyl)-2-methyl-1-oxo-1,2-dihydro-3-isooquinolinyl)methyl}-1H-isooindole-1,3(2H)-dione (synthesized according to the method similar to

³⁰ that in Example 4 (6))

Melting point 207-208°C.

Elemental analysis for C₂₆H₁₉N₂O₄Cl

Calculated: C, 68.05; H, 4.17; N, 6.10.

Found: C, 68.24; H, 4.25; N, 5.96.

³⁵ ¹H-NMR(DMSO-d₆) δ:3.58 (3H, s), 3.77 (3H, s), 4.77 (2H, s), 6.83 (1H, d, J=2.0 Hz), 6.98 (2H, d, J=8.8 Hz), 7.20

(2H, d, J=8.8 Hz), 7.55 (1H, dd, J=2.0, 8.6 Hz), 7.75-7.85 (4H, m), 8.29 (1H, d, J=8.6 Hz).

(7) Tert-butyl {6-chloro-4-(4-methoxyphenyl)-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl}methylcarbamate

⁵ (synthesized according to the method similar to that in Example 1 (6))

Melting point 187-188°C.

Elemental analysis for C₂₃H₂₅N₂O₄Cl

Calculated: C, 64.41; H, 5.88; N, 6.53.

¹⁰ Found: C, 64.72; H, 5.96; N, 6.51.

¹H-NMR(CDCl₃) δ: 1.43 (9H, s), 3.69 (3H, s), 3.91 (3H, s), 4.21 (2H, d, J=5.8 Hz), 4.65 (1H, bs), 6.95 (1H, d, J=2.0 Hz), 7.02 (2H, d, J=8.9 Hz), 7.15 (2H, d, J=8.9 Hz), 7.36 (1H, dd, J=2.0, 8.6 Hz), 8.35 (1H, d, J=8.6

¹⁵ Hz).

(8) 3-(Aminomethyl)-6-chloro-4-(4-methoxyphenyl)-2-methyl-1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7))

²⁰ Melting point 249-250°C.

Elemental analysis for C₁₈H₁₈N₂O₂Cl₂

Calculated: C, 59.19; H, 4.97; N, 7.67.

Found: C, 59.23; H, 4.81; N, 7.30.

¹H-NMR(DMSO-d₆) δ: 3.71 (3H, s), 3.87 (3H, s), 3.95 (2H, bs), 6.88 (1H, d, J=2.0 Hz), 7.14 (2H, d, J=8.8 Hz), 7.32 (2H, d, J=8.8 Hz), 7.62 (1H, dd, J=2.0, 8.6 Hz), 8.33 (1H, d, J=8.6 Hz), 8.66 (3H, bs).

Example 17

3-(Aminomethyl)-6-chloro-4-(3-methoxyphenyl)-2-methyl-

³⁰ 1(2H)-isoquinolinone hydrochloride

(1) Ethyl 6-chloro-4-(3-methoxyphenyl)-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 12 (2))

³⁵ Melting point 146-147°C.

Elemental analysis for C₂₀H₁₈NO₄Cl

Calculated: C, 64.61; H, 4.88; N, 3.77.

Found: C, 64.55; H, 4.84; N, 3.69.

¹H-NMR(CDCl₃) δ:0.97 (3H, t, J=7.2 Hz), 3.60 (3H, s), 3.83 (3H, s), 4.06 (2H, q, J=7.2 Hz), 6.84-7.09 (3H, m), 7.23 (1H, d, J=2.0 Hz), 7.37 (1H, t, J=7.9 Hz), 7.47 (1H, dd, J=2.0, 8.6 Hz), 8.44 (1H, d, J=8.6 Hz).

(2) 6-Chloro-4-(3-methoxyphenyl)-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4

10. (3))

Melting point 212-213°C.

Elemental analysis for C₁₈H₁₄NO₄Cl

Calculated: C, 62.89; H, 4.10; N, 4.07.

Found: C, 63.14; H, 4.22; N, 3.90.

15. ¹H-NMR(DMSO-d₆) δ:3.52 (3H, s), 3.78 (3H, s), 6.90-6.94 (2H, m), 7.03-7.07 (2H, m), 7.44 (1H, t, J=8.1 Hz), 7.62 (1H, dd, J=2.0, 8.6 Hz), 8.32 (1H, d, J=8.6 Hz)

(3) 6-Chloro-4-(3-methoxyphenyl)-3-hydroxymethyl-2-methyl-1(2H)-isoquinolinone (synthesized according to

20. the method similar to that in Example 4 (4))

Melting point 127-128°C.

Elemental analysis for C₁₈H₁₆NO₃Cl

Calculated: C, 65.56; H, 4.89; N, 4.25.

Found: C, 65.72; H, 5.14; N, 4.04.

25. ¹H-NMR(CDCl₃) δ:2.00 (1H, bs), 3.81 (3H, s), 3.86 (3H, s), 4.47 (2H, s), 6.82-6.89 (2H, m), 6.99-7.04 (2H, m), 7.38 (1H, dd, J=2.1, 8.6 Hz), 7.43 (1H, t, J=7.9 Hz), 8.37 (1H, d, J=8.6 Hz).

(4) 6-Chloro-3-chloromethyl-4-(3-methoxyphenyl)-2-

30. methyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

¹H-NMR(CDCl₃) δ:3.82 (3H, s), 3.86 (3H, s), 4.40 (2H, s), 6.88-6.92 (1H, m), 7.01-7.07 (2H, m), 7.44 (1H, dd, J=2.0, 8.6 Hz), 7.45 (1H, t, J=8.0 Hz), 8.42 (1H, d, J=8.6 Hz).

35. (5) 2-{(6-Chloro-4-(3-methoxyphenyl)-2-methyl-1-oxo-1,2-

dihydro-3-isoquinolinyl)methyl}-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

Melting point 184-185°C.

⁵ Elemental analysis for C₂₆H₁₉N₂O₄Cl

Calculated: C, 68.05; H, 4.17; N, 6.10.

Found: C, 67.69; H, 4.40; N, 5.82.

¹H-NMR(DMSO-d₆) δ:3.61 (3H, s), 3.63 (3H, s), 4.78 (2H, s), 6.08-6.84 (3H, m), 6.90-6.95 (1H, m), 7.33 (1H, t, J=8.1 Hz), 7.55 (1H, dd, J=2.0, 8.6 Hz), 7.74-7.84 (4H, m), 8.30 (1H, d, J=8.6 Hz).

(6) Tert-butyl {6-chloro-4-(3-methoxyphenyl)-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in

¹⁵ Example 1 (6)).

Melting point 231-232°C.

Elemental analysis for C₂₃H₂₅N₂O₄Cl

Calculated: C, 64.41; H, 5.88; N, 6.53.

Found: C, 64.25; H, 5.49; N, 6.34.

²⁰ ¹H-NMR(CDCl₃) δ:1.43 (9H, s), 3.70 (3H, s), 3.86 (3H, s), 4.21-4.23 (2H, m), 4.60 (1H, bs), 6.77-6.84 (2H, m); 6.96 (1H, d, J=1.8 Hz), 6.99-7.05 (1H, m), 7.35-7.48 (2H, m), 8.37 (1H, d, J=8.8 Hz).

(7) 3-(Aminomethyl)-6-chloro-4-(3-methoxyphenyl)-2-

²⁵ methyl-1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7)).

Melting point 237-238°C.

Elemental analysis for C₁₈H₁₈N₂O₂Cl₂ 1/2H₂O

³⁰ Calculated: C, 57.77; H, 5.12; N, 7.67.

Found: C, 57.62; H, 5.23; N, 7.40.

¹H-NMR(DMSO-d₆) δ:3.71 (3H, s), 3.82 (3H, s), 3.92-3.98 (2H, m), 6.87 (1H, d, J=2.0 Hz), 6.94 (1H, d, J=7.5 Hz), 7.01 (1H, bs), 7.11 (1H, dd, J=2.6, 8.1 Hz), 7.51 (1H,

³⁵ dd, J=7.5, 8.1 Hz), 7.62 (1H, dd, J=2.0, 8.6 Hz), 8.33 (1H, d, J=8.6 Hz), 8.63 (3H, bs).

Example 18

3-(Aminomethyl)-6-chloro-4-(4-hydroxyphenyl)-2-methyl-1(2H)-isoquinolinone hydrochloride

(1) To a solution of 2-{{[6-chloro-4-(4-methoxyphenyl)-2-methyl-1-oxo-1,2-dihydro-3-isooquinolinyl]methyl}-1H-isooindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 16 (7)) (0.92 g, 2 mmol) in dichloromethane (10 ml) was added boron tribromide (0.76 ml, 36 mmol) at 0°C and the mixture was stirred at 0°C for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from tetrahydrofuran - diisopropyl ether to give 2-{{[6-chloro-4-(4-hydroxyphenyl)-2-methyl-1-oxo-1,2-dihydro-3-isooquinolinyl]methyl}-1H-isooindole-1,3(2H)-dione (0.83 g, 94.3%) as crystals.

Melting point 307-308°C.

Elemental analysis for $C_{25}H_{17}N_2O_4Cl\ H_2O$

Calculated: C, 64.87; H, 4.14; N, 6.05.

Found: C, 64.44; H, 3.88; N, 5.66.

1H -NMR(DMSO-d₆) δ : 3.67 (3H, s), 4.76 (2H, s), 6.81 (2H, d, J=8.6 Hz), 6.86 (1H, d, J=2.0 Hz), 7.08 (2H, d, J=8.6 Hz), 7.54 (1H, dd, J=2.0, 8.6 Hz), 7.75-7.85 (4H, m), 8.28 (1H, d, J=8.6 Hz), 9.60 (1H, s).

(2) Tert-butyl 4-{{3-{{(tert-butoxycarbonyl)amino}methyl}-6-chloro-2-methyl-1-oxo-1,2-dihydro-3-isooquinolinyl}phenylcarbonate (synthesized according to the method similar to that in Example 1 (6))

Melting point 195-196°C.

Elemental analysis for $C_{27}H_{31}N_2O_6Cl$

Calculated: C, 62.97; H, 6.07; N, 5.44.

Found: C, 63.02; H, 6.28; N, 5.34.

1H -NMR(CDCl₃) δ : 1.41 (9H, s), 1.61 (9H, s), 3.69 (3H, s),

4.20 (2H, d, J=6.0 Hz), 4.62 (1H, bs), 6.92 (1H, d, J=1.8 Hz), 7.24-7.40 (5H, m), 8.35 (1H, d, J=8.6 Hz).

(3) 3-(Aminomethyl)-6-chloro-4-(4-hydroxyphenyl)-2-methyl-1(2H)-isoquinolinone hydrochloride (synthesized

5 according to the method similar to that in Example 1 (7))

Melting point 253-254°C.

Elemental analysis for C₁₇H₁₆N₂O₂Cl₂

Calculated: C, 58.13; H, 4.59; N, 7.98.

10 Found: C, 57.99; H, 4.57; N, 7.88.

¹H-NMR(DMSO-d₆) δ:3.70 (3H, s), 3.97 (2H, bs), 6.92 (1H, d, J=2.0 Hz), 6.97 (2H, d, J=8.4 Hz), 7.17 (2H, d, J=8.4 Hz), 7.60 (1H, dd, J=2.0, 8.6 Hz), 8.32 (1H, d, J=8.6 Hz), 8.62 (3H, bs), 9.89 (1H, bs).

15. Example 19

3-(Aminomethyl)-6-chloro-4-(3-hydroxyphenyl)-2-methyl-1(2H)-isoquinolinone hydrochloride

(1) 2-{{[6-Chloro-4-(3-hydroxyphenyl)-2-methyl-1-oxo-1,2-dihydro-3-isooquinolinyl]methyl}-1H-isoindole-1,3(2H)-

20 dione (synthesized according to the method similar to that in Example 18 (1))

Melting point 297-298°C.

Elemental analysis for C₂₅H₁₇N₂O₄Cl 1/4H₂O

Calculated: C, 66.82; H, 4.00; N, 6.23.

25 Found: C, 66.52; H, 4.34; N, 5.85.

¹H-NMR(DMSO-d₆) δ:3.58 (3H, s), 4.73 (1H, d, J=15.8 Hz), 4.82 (1H, d, J=15.8 Hz), 6.65-6.70 (2H, m), 6.76-6.80 (1H, m), 6.85 (1H, d, J=2.0 Hz), 7.20 (1H, t, J=7.7 Hz), 7.55 (1H, dd, J=2.0, 8.6 Hz), 7.75-7.85 (4H, m), 8.29

30 (1H, d, J=8.6 Hz), 9.57 (1H, s).

(2) Tert-butyl {6-chloro-4-(3-hydroxyphenyl)-2-methyl-1-oxo-1,2-dihydro-3-isooquinolinyl}methylcarbamate

(synthesized according to the method similar to that in Example 1 (6))

35 Melting point 244-245°C.

Elemental analysis for C₂₂H₂₃N₂O₄Cl

Calculated: C, 63.69; H, 5.59; N, 6.75.

Found: C, 63.76; H, 5.75; N, 6.52.

¹H-NMR(CDCl₃) δ: 1.44 (9H, s), 3.69 (3H, s), 4.23 (2H, d, J=5.6 Hz), 4.86 (1H, bs), 6.69-6.75 (2H, m), 6.95-7.00

⁵ (1H, m), 7.02 (1H, d, J=2.0 Hz), 7.33 (1H, t, J=7.7 Hz), 7.37 (1H, dd, J=2.0, 8.6 Hz), 8.36 (1H, d, J=8.6 Hz), 8.87 (1H, s).

(3) 3-(Aminomethyl)-6-chloro-4-(3-hydroxyphenyl)-2-methyl-1(2H)-isoquinolinone hydrochloride (synthesized
¹⁰ according to the method similar to that in Example 1 (7))

Melting point 277°C.

Elemental analysis for C₁₇H₁₆N₂O₂Cl₂

Calculated: C, 58.13; H, 4.59; N, 7.98.

¹⁵ Found: C, 57.96; H, 4.66; N, 8.01.
¹H-NMR(DMSO-d₆) δ: 3.69 (3H, s), 3.97 (2H, bs), 6.78-6.81 (2H, m), 6.90 (1H, d, J=2.0 Hz), 6.94-6.99 (1H, m), 7.38 (1H, t, J=7.9 Hz), 7.62 (1H, dd, J=2.0, 8.6 Hz), 8.32 (1H, d, J=8.6 Hz), 8.60 (3H, bs), 9.87 (1H, bs).

²⁰ Example 20

3-(Aminomethyl)-6-chloro-4-(4-fluorophenyl)-2-methyl-1(2H)-isoquinolinone hydrochloride

(1) Ethyl 6-chloro-4-(4-fluorophenyl)-2-methyl-1-oxo-1,2-dihydro-3-isouinolinecarboxylate (synthesized

²⁵ according to the method similar to that in Example 12 (2))

Melting point 159-160°C.

Elemental analysis for C₁₉H₁₅NO₃ClF

Calculated: C, 63.43; H, 4.20; N, 3.89.

³⁰ Found: C, 63.56; H, 3.96; N, 3.66.

¹H-NMR(CDCl₃) δ: 1.00 (3H, t, J=7.0 Hz), 3.59 (3H, s), 4.07 (2H, q, J=7.0 Hz), 7.12 (1H, d, J=2.0 Hz), 7.17-7.21 (2H, m), 7.27-7.347 (2H, m), 7.48 (1H, dd, J=2.0, 8.6 Hz), 8.44 (1H, d, J=8.6 Hz).

³⁵ (2) 6-Chloro-4-(4-fluorophenyl)-2-methyl-1-oxo-1,2-dihydro-3-isouinolinecarboxylic acid (synthesized

according to the method similar to that in Example 4
(3))

Melting point 239-240°C.

Elemental analysis for C₁₇H₁₁NO₃ClF

⁵ Calculated: C, 61.55; H, 3.34; N, 4.22.

Found: C, 61.82; H, 3.52; N, 4.02.

¹H-NMR(DMSO-d₆) δ:3.52 (3H, s), 6.99 (1H, d, J=2.0 Hz), 7.30-7.45 (4H, m), 7.63 (1H, dd, J=2.0, 8.6 Hz), 8.33 (1H, d, J=8.6 Hz).

¹⁰ (3) 6-Chloro-4-(4-fluorophenyl)-3-hydroxymethyl-2-methyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))

Melting point 167-168°C.

Elemental analysis for C₁₇H₁₃NO₂ClF

¹⁵ Calculated: C, 64.26; H, 4.12; N, 4.41.

Found: C, 64.33; H, 4.08; N, 4.36.

¹H-NMR(CDCl₃) δ:2.08 (1H, bs), 3.81 (3H, s), 4.45 (2H, d, J=5.2 Hz), 6.94 (1H, d, J=2.0 Hz), 7.17-7.33 (4H, m), 7.38 (1H, d, J=2.0, 8.6 Hz), 8.36 (1H, d, J=8.6 Hz).

²⁰ (4) 6-Chloro-3-chloromethyl-4-(4-fluorophenyl)-2-methyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

¹H-NMR(CDCl₃) δ:3.82 (3H, s), 4.37 (2H, s), 6.97 (1H, d, J=2.0 Hz), 7.20-7.37 (4H, m), 7.45 (1H, dd, J=2.0, 8.6

²⁵ Hz), 8.43 (1H, d, J=8.6 Hz).

(5) 2-[{6-Chloro-4-(4-fluorophenyl)-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methyl}-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

³⁰ Melting point 190-191°C.

Elemental analysis for C₂₅H₁₆N₂O₃ClF

Calculated: C, 67.20; H, 3.61; N, 6.27.

Found: C, 67.40; H, 3.42; N, 6.24.

¹H-NMR(DMSO-d₆) δ:3.61 (3H, s), 4.75 (2H, s), 6.78 (1H,

³⁵ d, J=2.0 Hz), 7.23-7.39 (4H, m), 7.57 (1H, dd, J=2.0, 8.6 Hz), 7.76-7.85 (4H, m), 7.86 (4H, s), 8.31 (1H, d,

J=8.6 Hz).

(6) Tert-butyl {6-chloro-4-(4-fluorophenyl)-2-methyl-1-oxo-1,2-dihydro-3-isouquinolinyl}methylcarbamate

(synthesized according to the method similar to that in

5 Example 1 (6))

Melting point 206-207°C.

Elemental analysis for C₂₂H₂₂N₂O₃ClF

Calculated: C, 63.39; H, 5.32; N, 6.72.

Found: C, 63.56; H, 5.27; N, 6.61.

10 ¹H-NMR(CDCl₃) δ:1.44 (9H, s), 3.69 (3H, s), 4.19 (2H, d, J=5.6 Hz), 4.67 (1H, bs), 6.88 (1H, d, J=2.0 Hz), 7.22-7.27 (4H, m), 7.38 (1H, dd, J=2.0, 8.6 Hz), 8.35 (1H, d, J=8.6 Hz).

(7) 3-(Aminomethyl)-6-chloro-4-(4-fluorophenyl)-2-methyl-1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 277-278°C.

Elemental analysis for C₁₇H₁₅N₂OCl₂F

20 Calculated: C, 57.81; H, 4.28; N, 7.93.

Found: C, 57.98; H, 4.29; N, 7.84.

¹H-NMR(DMSO-d₆): δ:3.71 (3H, s), 3.92 (2H, s), 6.83 (1H, d, J=2.0 Hz), 7.37-7.46 (4H, m), 7.62 (1H, dd, J=2.0, 8.6 Hz), 8.34 (1H, d, J=8.6 Hz), 8.73 (3H, bs).

25 Example 21

3-(Aminomethyl)-6-chloro-2-methyl-4-(4-trifluoromethylphenyl)-1(2H)-isoquinolinone hydrochloride

(1) 6-Chloro-2-methyl-1-oxo-4-(4-trifluoromethylphenyl)-30 1,2-dihydro-3-isouquinolinecarboxylate ethyl (synthesized according to the method similar to that in Example 12 (2))

Melting point 170-171°C.

Elemental analysis for C₂₀H₁₅NO₃ClF₃

35 Calculated: C, 58.62; H, 3.69; N, 3.40.

Found: C, 58.83; H, 3.71; N, 3.22.

¹H-NMR(CDCl₃) δ: 0.93 (3H, t, J=7.2 Hz), 3.60 (3H, s), 4.05 (2H, q, J=7.2 Hz), 7.09 (1H, d, J=2.0 Hz), 7.46 (2H, d, J=7.8 Hz), 7.50 (1H, dd, J=2.0, 8.4 Hz), 7.75 (2H, d, J=7.8 Hz), 8.46 (1H, d, J=8.4 Hz).

- 5 (2) 6-Chloro-2-methyl-1-oxo-4-(4-trifluoromethylphenyl)-1,2-dihydro-3-isooquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))

Melting point 285-286°C.

- 10 Elemental analysis for C₁₈H₁₁NO₃ClF₃, Calculated: C, 56.63; H, 2.90; N, 3.67. Found: C, 56.73; H, 2.68; N, 3.49.

¹H-NMR(DMSO-d₆) δ: 3.53 (3H, s), 6.99 (1H, d, J=2.2 Hz), 7.60 (2H, d, J=8.0 Hz), 7.65 (1H, dd, J=2.2, 8.4 Hz),

- 15 7.89 (2H, d, J=8.0 Hz), 8.34 (1H, d, J=8.4 Hz).

(3) 6-Chloro-3-hydroxymethyl-2-methyl-4-(4-trifluoromethylphenyl)-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))

- 20 Melting point 219-220°C.

Elemental analysis for C₁₈H₁₃NO₂ClF₃,

Calculated: C, 58.79; H, 3.56; N, 3.81.

Found: C, 58.94; H, 3.52; N, 3.65.

¹H-NMR(CDCl₃) δ: 2.13 (1H, bs), 3.82 (3H, s), 4.43 (2H, d,

- 25 J=5.0 Hz), 7.40 (1H, dd, J=2.0, 8.6 Hz), 7.47 (2H, d, J=7.9 Hz), 7.80 (2H, d, J=7.9 Hz), 8.37 (1H, d, J=8.6 Hz).

(4) 6-Chloro-3-chloromethyl-2-methyl-4-(4-trifluoromethylphenyl)-1(2H)-isoquinolinone (synthesized

- 30 according to the method similar to that in Example 4 (5))

¹H-NMR(CDCl₃) δ: 3.83 (3H, s), 4.33 (2H, s), 6.91 (1H, d, J=1.8 Hz), 7.47 (1H, dd, J=1.8, 8.6 Hz), 7.50 (2H, d, J=7.5 Hz), 7.83 (2H, d, J=7.5 Hz), 8.45 (1H, d, J=8.6

- 35 Hz).

(5) 2-{(6-Chloro-2-methyl-1-oxo-4-(4-

trifluoromethylphenyl)-1,2-dihydro-3-isoquinolinyl)methyl}-1H-isoindole-1,3(2H)-dione
(synthesized according to the method similar to that in Example 4 (6))

⁵ Melting point 236-237°C.

Elemental analysis for C₂₆H₁₆N₂O₃ClF₃

Calculated: C, 62.85; H, 3.25; N, 5.64.

Found: C, 62.92; H, 3.07; N, 5.52.

¹H-NMR(DMSO-d₆) δ:3.62 (3H, s), 4.76 (2H, s), 6.73 (1H, d, J=1.8 Hz), 7.54 (2H, d, J=7.6 Hz), 7.58 (1H, dd, J=1.8, 8.4 Hz), 7.73-7.84 (6H, m), 8.32 (1H, d, J=8.4 Hz).

(6) Tert-butyl {6-chloro-2-methyl-1-oxo-4-(4-trifluoromethylphenyl)-1,2-dihydro-3-isoquinolinyl}-methylcarbamate (synthesized according to the method similar to that in Example 1 (6))

Melting point 193-194°C.

Elemental analysis for C₂₃H₂₂N₂O₃ClF₃

Calculated: C, 59.17; H, 4.75; N, 6.00.

²⁰ Found: C, 59.35; H, 4.76; N, 5.92.
¹H-NMR(CDCl₃) δ:1.43 (9H, s), 3.70 (3H, s), 4.16 (2H, d, J=5.8 Hz), 4.67 (1H, bs), 6.82 (1H, d, J=2.0 Hz), 7.39 (1H, dd, J=2.0, 8.6 Hz), 7.42 (2H, d, J=7.9 Hz), 7.81 (2H, d, J=7.9 Hz), 8.36 (1H, d, J=8.6 Hz).

(7) 3-(Aminomethyl)-6-chloro-2-methyl-4-(4-trifluoromethylphenyl)-1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 261-262°C.

³⁰ Elemental analysis for C₁₈H₁₅N₂OCl₂F₃ 1/2H₂O

Calculated: C, 52.44; H, 3.91; N, 6.80.

Found: C, 52.57; H, 4.09; N, 7.02.

³⁵ ¹H-NMR(DMSO-d₆) δ:3.71 (3H, s), 3.90 (2H, s), 6.79 (1H, d, J=2.0 Hz), 7.64 (1H, dd, J=2.0, 8.8 Hz), 7.65 (2H, d, J=8.2 Hz), 7.96 (2H, d, J=8.2 Hz), 8.35 (1H, d, J=8.8 Hz), 8.70 (3H, bs).

Example 22

3-(Aminomethyl)-6,7-dichloro-2-methyl-4-phenyl-1(2H)-isoquinolinone hydrochloride

- (1) ethyl 6,7-dichloro-4-hydroxy-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 4 (1))
Melting point 127-128°C.

Elemental analysis for $C_{13}H_{11}NO_4Cl_2$

Calculated: C, 49.39; H, 3.51; N, 4.43.

Found: C, 49.31; H, 3.50; N, 4.36.

1H -NMR(CDCl₃) δ:1.47 (3H, t, J=7.2 Hz), 3.68 (3H, s), 4.51 (2H, q, J=7.2 Hz), 8.21 (1H, s), 8.51 (1H, bs), 11.17 (1H, s).

(2) Ethyl 6,7-dichloro-2-methyl-1-oxo-4-

- trifluoromethanesulfonyloxy-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 12 (1))

1H -NMR(CDCl₃) δ:1.45 (3H, t, J=7.2 Hz), 3.60 (3H, s), 4.49 (2H, q, J=7.2 Hz), 7.86 (1H, s), 8.53 (1H, s).

- (3) Ethyl 6,7-dichloro-2-methyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 12 (2))
Melting point 288-289°C.

Elemental analysis for $C_{19}H_{15}NO_3Cl_2$

Calculated: C, 60.65; H, 4.02; N, 3.72.

Found: C, 60.96; H, 4.04; N, 3.62.

1H -NMR(CDCl₃) δ:0.92 (3H, t, J=7.2 Hz), 3.60 (3H, s), 4.02 (2H, q, J=7.2 Hz), 7.28-7.32 (3H, m), 7.45-7.48 (3H, m), 8.57 (1H, s).

- (4) 6,7-Dichloro-2-methyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))
Melting point 261-262°C.

1H -NMR(CDCl₃) δ:3.68 (3H, s), 7.13 (1H, d, J=8.8 Hz),

7.32-7.51 (6H, m), 8.45 (1H, d, J=2.2 Hz).

(5) 6,7-Dichloro-3-hydroxymethyl-2-methyl-4-phenyl-

1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))

Melting point 211-212°C.

Elemental analysis for C₁₇H₁₃NO₂Cl₂

⁵ Calculated: C, 61.10; H, 3.92; N, 4.19.

Found: C, 61.21; H, 3.80; N, 4.12.

¹H-NMR(CDCl₃) δ:2.22 (1H, t, J=5.8 Hz), 3.81 (3H, s), 4.45 (2H, d, J=5.8 Hz), 7.09 (1H, s), 7.27-7.33 (2H, m), 7.48-7.56 (3H, m), 8.47 (1H, s).

¹⁰ (6) 6,7-Dichloro-3-chloromethyl-2-methyl-4-phenyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

¹H-NMR(CDCl₃) δ:3.82 (3H, s), 4.36 (2H, s), 7.11 (1H, s), 7.31-7.34 (2H, m), 7.49-7.56 (3H, m), 8.57 (1H, s).

¹⁵ (7) 2-{(6,7-Dichloro-2-methyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methyl}-1H-isoindole-1,3(2H)-dione. (synthesized according to the method similar to that in Example 4 (6))

Melting point 234-235°C.

²⁰ Elemental analysis for C₂₅H₁₆N₂O₃Cl₂

Calculated: C, 64.81; H, 3.48; N, 6.05.

Found: C, 64.68; H, 3.56; N, 5.86.

¹H-NMR(DMSO-d₆) δ:3.61 (3H, s), 4.76 (2H, s), 6.94 (1H, s), 7.28-7.32 (2H, m), 7.41-7.48 (3H, m), 8.40 (1H, s).

²⁵ (8) Tert-butyl {6,7-dichloro-2-methyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl}methylcarbamate (synthesized according to the method similar to that in Example 1 (6))

Melting point 226-227°C.

³⁰ Elemental analysis for C₂₂H₂₂N₂O₃Cl₂

Calculated: C, 60.98; H, 5.12; N, 6.46.

Found: C, 61.10; H, 5.30; N, 6.37.

¹H-NMR(CDCl₃) δ:1.43 (9H, s), 3.70 (3H, s), 4.19 (2H, d, J=5.4 Hz), 4.77 (1H, bs), 7.02 (1H, s), 7.22-7.27 (2H, m), 7.49-7.53 (3H, m), 8.47 (1H, s).

³⁵ (9) 3-(Aminomethyl)-6,7-dichloro-2-methyl-4-phenyl-

1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 4 (7))

Melting point 266-267°C.

⁵ Elemental analysis for C₁₇H₁₅N₂OCl₃

Calculated: C, 55.23; H, 4.09; N, 7.58.

Found: C, 55.40; H, 4.21; N, 7.33.

¹H-NMR(DMSO-d₆) δ:3.72 (3H, s), 3.93 (2H, bs), 6.99 (1H, s), 7.39-7.44 (2H, m), 7.55-7.64 (3H, m), 8.43 (1H, s),

¹⁰ 8.73 (3H, bs).

Example 23

3-(Aminomethyl)-6-chloro-2-methyl-4-(3-nitrophenyl)-1(2H)-isoquinolinone hydrochloride

(1) Ethyl 6-chloro-2-methyl-1-oxo-4-(3-nitrophenyl)-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according

to the method similar to that in Example 12 (2))

Melting point 211-212°C.

Elemental analysis for C₁₉H₁₅N₂O₅Cl

Calculated: C, 59.00; H, 3.91; N, 7.24.

²⁰ Found: C, 59.13; H, 3.86; N, 7.32.

¹H-NMR(CDCl₃) δ:1.02 (3H, t, J=7.2 Hz), 3.61 (3H, s), 4.09 (2H, q, J=7.2 Hz), 7.02 (1H, d, J=2.0 Hz), 7.52 (1H, dd, J=2.0, 8.6 Hz), 7.68-7.71 (2H, m), 8.23-8.25 (1H, m), 8.32-8.38 (1H, m), 8.47 (1H, d, J=8.6 Hz).

²⁵ (2) 6-Chloro-2-methyl-1-oxo-4-(3-nitrophenyl)-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))

Melting point 259-260°C.

³⁰ ¹H-NMR(CDCl₃) δ:3.54 (3H, s), 7.04 (1H, d, J=2.0 Hz), 7.65 (1H, dd, J=2.0, 8.6 Hz), 7.82-7.85 (2H, m), 8.19-8.21 (1H, m), 8.33-8.39 (2H, m).

(3) 6-Chloro-3-hydroxymethyl-2-methyl-4-(3-nitrophenyl)-1(2H)-isoquinolinone (synthesized according to the

³⁵ method similar to that in Example 4 (4))

Melting point 227-228°C.

Elemental analysis for C₁₇H₁₃N₂O₄Cl 1/2H₂O

Calculated: C, 57.72; H, 3.99; N, 7.92.

Found: C, 57.96; H, 3.88; N, 7.63.

¹H-NMR(CDCl₃) δ: 3.85 (3H, s), 4.34 (2H, d, J=3.2 Hz),

5 4.80 (1H, bs), 6.86 (1H, d, J=2.0 Hz), 7.42 (1H, dd, J=2.0, 8.6 Hz), 7.69-7.73 (2H, m), 8.27-8.38 (2H, m), 8.43 (1H, d, J=8.6 Hz).

(4) 6-Chloro-3-chloromethyl-2-methyl-4-(3-nitrophenyl)-1(2H)-isoquinolinone (synthesized according to the

10 method similar to that in Example 4 (5))

¹H-NMR(CDCl₃) δ: 3.84 (3H, s), 4.32 (2H, s), 6.86 (1H, d, J=2.0 Hz), 7.49 (1H, dd, J=2.0, 8.6 Hz), 7.73-7.79 (2H, m), 8.25-8.26 (1H, m), 8.39-8.43 (1H, m), 8.46 (1H, d, J=8.6 Hz).

15 (5) 2-{(6-Chloro-2-methyl-1-oxo-4-(3-nitrophenyl)-1,2-dihydro-3-isooquinolinyl)methyl}-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

Melting point 246-247°C.

20 Elemental analysis for C₂₅H₁₆N₃O₅Cl

Calculated: C, 63.37; H, 3.40; N, 8.87.

Found: C, 63.14; H, 3.33; N, 8.50.

¹H-NMR(DMSO-d₆) δ: 3.65 (3H, s), 4.71 (1H, d, J=16.3 Hz), 4.80 (1H, d, J=16.3 Hz), 6.79 (1H, d, J=2.0 Hz), 7.59

25 (1H, d, J=2.0, 8.6 Hz), 7.69-7.84 (5H, m), 8.13-8.14 (1H, m), 8.23-8.29 (4H, m), 8.33 (1H, d, J=8.6 Hz).

(6) Tert-butyl {6-chloro-2-methyl-1-oxo-4-(3-nitrophenyl)-1,2-dihydro-3-isooquinolinyl)methylcarbamate (synthesized according to the method similar to that in

30 Example 1 (6))

Melting point 231-232°C.

Elemental analysis for C₂₂H₂₂N₃O₅Cl

Calculated: C, 59.53; H, 5.00; N, 9.47.

Found: C, 59.51; H, 5.01; N, 9.25.

35 ¹H-NMR(CDCl₃) δ: 1.42 (9H, s), 3.71 (3H, s), 4.14-4.17 (2H, m), 4.81 (1H, bs), 6.77 (1H, s), 7.18-7.23 (1H, m),

7.62 (1H, d, J=7.8 Hz), 7.76 (1H, t, J=7.8 Hz), 8.17 (1H, s), 8.36-8.42 (2H, m).

(7) 3-(Aminomethyl)-6-chloro-2-methyl-4-(3-nitrophenyl)-1(2H)-isoquinolinone hydrochloride (synthesized

5 according to the method similar to that in Example 1
(7))

Melting point 263-264°C.

Elemental analysis for C₁₇H₁₅N₃O₃Cl₂

Calculated: C, 53.70; H, 3.98; N, 11.05.

10 Found: C, 53.56; H, 4.09; N, 10.95.

¹H-NMR(DMSO-d₆) δ:3.71 (3H, s), 3.83-3.93 (2H, m), 36.86 (1H, d, J=2.0 Hz), 7.65 (1H, dd, J=2.0, 8.6 Hz), 7.82-7.93 (2H, m), 8.23-8.25 (1H, m), 8.35 (1H, d, J=8.6 Hz), 8.39-8.44 (1H, m), 8.66 (3H, bs).

15 Example 24

3-(Aminomethyl)-4-(3-aminophenyl)-6-chloro-2-methyl-1(2H)-isoquinolinone hydrochloride

(1) Tert-butyl {6-chloro-2-methyl-1-oxo-4-(3-nitrophenyl)-1,2-dihydro-3-isooquinolinyl}methylcarbamate

20 synthesized according to the method similar to that in Example 23 (6) (0.89 g, 2 mmol) was added to an aqueous solution (10 ml) of potassium carbonate (2.90 g, 21 mmol) and sodium hydrosulfite (2.44 g, 14 mmol) and the mixture was stirred at room temperature for 1 h. The

25 reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography

30 to give tert-butyl {4-(3-aminophenyl)-6-chloro-2-methyl-1-oxo-1,2-dihydro-3-isooquinolinyl}methylcarbamate (0.48 g, 58.5%) as crystals.

Melting point 157-158°C.

¹H-NMR(CDCl₃) δ:1.43 (9H, s), 3.69 (3H, s), 4.22 (2H, d,

35 J=5.6 Hz), 4.65 (1H, bs), 6.54-6.62 (1H, m), 6.76-6.83 (1H, m), 6.90-7.03 (1H, m), 7.08 (1H, dd, J=2.0, 8.0 Hz),

7.34-7.45 (2H, m), 8.35 (1H, d, J=8.0 Hz).

(2) 3-(Aminomethyl)-4-(3-aminophenyl)-6-chloro-2-methyl-1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1

5 (7))

Melting point 255°C.

Elemental analysis for $C_{17}H_{18}N_3OCl_3 \cdot 1/2H_2O$

Calculated: C, 51.60; H, 4.84; N, 10.62.

Found: C, 51.76; H, 4.64; N, 10.29.

10 1H -NMR(DMSO-d₆) δ:3.70 (3H, s), 3.91 (2H, bs), 6.87-6.93 (2H, m), 7.38-7.46 (1H, m), 7.57-7.75 (3H, m), 8.35 (1H, d, J=8.8 Hz), 8.73-8.87 (6H, m).

Example 25

3-(Aminomethyl)-4-butoxy-6-chloro-2-propyl-1(2H)-15 isoquinolinone hydrochloride

(1) Ethyl 6-chloro-4-hydroxy-1-oxo-2-propyl-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (1))

Melting point 61-62°C.

20 Elemental analysis for $C_{15}H_{16}NO_4Cl$

Calculated: C, 58.16; H, 5.21; N, 4.52.

Found: C, 58.22; H, 5.28; N, 4.45.

1H -NMR(CDCl₃) δ:0.93 (3H, t, J=7.3 Hz), 1.47 (3H, t, J=7.2 Hz), 1.69-1.84 (2H, m), 4.17-4.24 (2H, m), 4.51

25 (2H, q, J=7.2 Hz), 7.62 (1H, dd, J=2.2, 8.6 Hz), 8.11 (1H, d, J=2.2 Hz), 8.37 (1H, d, J=2.2 Hz), 11.28 (1H, s).

(2) Ethyl 4-butoxy-6-chloro-1-oxo-2-propyl-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (2))

30 Melting point 72-73°C.

Elemental analysis for $C_{19}H_{24}NO_4Cl$

Calculated: C, 62.38; H, 6.61; N, 3.83.

Found: C, 62.32; H, 6.55; N, 3.56.

1H -NMR(CDCl₃) δ:0.94 (3H, t, J=7.3 Hz), 1.01 (3H, t,

35 J=7.3 Hz), 1.43 (3H, t, J=7.1 Hz), 1.48-1.62 (2H, m), 1.68-1.86 (4H, m), 3.85-3.98 (4H, m), 4.47 (2H, q, J=7.1

Hz), 7.49 (1H, dd, J=2.0, 8.7 Hz), 7.69 (1H, d, J=2.0 Hz), 8.37 (1H, d, J=8.7 Hz).

(3) 4-Butoxy-6-chloro-1-oxo-2-propyl-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to

⁵ the method similar to that in Example 4 (3))

Melting point 175-176°C.

Elemental analysis for C₁₇H₂₀NO₄Cl

Calculated: C, 60.45; H, 5.97; N, 4.15.

Found: C, 60.45; H, 6.27; N, 3.98.

¹⁰ ¹H-NMR(CDCl₃) δ:0.91-1.06 (6H, m), 1.50-1.65 (2H, m), 1.80-1.85 (4H, m), 3.95-4.04 (4H, m), 7.46 (1H, dd, J=2.0, 8.6 Hz), 7.70 (1H, d, J=2.0 Hz), 8.36 (1H, d, J=8.6 Hz).

(4) 4-Butoxy-6-chloro-3-hydroxymethyl-2-propyl-1(2H)-

¹⁵ isoquinolinone (synthesized according to the method similar to that in Example 4 (4))

Melting point 108-109°C.

Elemental analysis for C₁₇H₂₂NO₃Cl

Calculated: C, 63.06; H, 6.85; N, 4.33.

²⁰ Found: C, 62.75; H, 6.89; N, 4.12.

¹H-NMR(CDCl₃) δ:1.00 (3H, t, J=7.6 Hz), 1.04 (3H, t, J=7.0 Hz), 1.49-1.92 (6H, m), 2.43 (2H, t, J=6.6 Hz), 4.79 (1H, t, J=5.6 Hz), 3.87 (2H, t, J=6.6 Hz), 4.12-4.20 (2H, m), 4.79 (2H, d, J=5.6 Hz), 7.41 (1H, dd, J=2.0, 8.6 Hz), 7.61 (1H, d, J=2.0 Hz), 8.29 (1H, d, J=8.6 Hz)..

(5) 4-Butoxy-6-chloro-3-chloromethyl-2-propyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

³⁰ ¹H-NMR(CDCl₃) δ:1.02 (3H, t, J=7.4 Hz), 1.05 (3H, t, J=7.2 Hz), 1.56-1.97 (6H, m), 3.99 (2H, t, J=6.5 Hz), 4.11-4.19 (2H, m), 4.78 (2H, s), 7.47 (1H, dd, J=2.2, 8.6 Hz), 7.70 (1H, d, J=2.2 Hz), 8.37 (1H, d, J=8.6 Hz).

(6) 2-((4-Butoxy-6-chloro-1-oxo-2-propyl-1,2-dihydro-3-

³⁵ isoquinolinyl)methyl)-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in

Example 4 (6))

Melting point 153-154°C.

Elemental analysis for C₂₅H₂₅N₂O₄Cl

Calculated: C, 66.29; H, 5.56; N, 6.18.

⁵ Found: C, 66.31; H, 5.48; N, 6.08.

¹H-NMR(DMSO-d₆) δ:0.80 (3H, t, J=7.3 Hz), 0.92 (3H, t, J=7.4 Hz), 1.38-1.58 (4H, m), 1.69-1.82 (2H, m), 3.89-4.02 (4H, m), 5.02 (2H, s), 7.59 (1H, dd, J=2.0, 8.6 Hz), 7.65 (1H, d, J=2.0 Hz), 7.83-7.92 (4H, m), 8.24 (1H, d, J=8.6 Hz).

¹⁰ J=8.6 Hz).

(7) Tert-butyl (4-butoxy-6-chloro-1-oxo-2-propyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 1 (6))

¹⁵ Melting point 120-121°C.

Elemental analysis for C₂₂H₃₁N₂O₄Cl

Calculated: C, 62.48; H, 7.39; N, 6.62.

Found: C, 62.53; H, 7.40; N, 6.49.

¹H-NMR(CDCl₃) δ:1.01 (3H, t, J=7.4 Hz), 1.04 (3H, t, J=6.8 Hz), 1.47 (9H, s), 1.52-1.90 (4H, m), 3.84 (2H, t, J=6.6 Hz), 4.01-4.08 (2H, m), 4.50 (2H, d, J=5.6 Hz), 4.77 (1H, bs), 7.43 (1H, dd, J=2.0, 8.6 Hz), 7.64 (1H, d, J=2.0 Hz), 8.34 (1H, d, J=8.6 Hz).

(8) 3-(Aminomethyl)-4-butoxy-6-chloro-2-propyl-1(2H)-²⁵ isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 124-125°C.

Elemental analysis for C₁₇H₂₄N₂O₂Cl₂ 1/4H₂O

Calculated: C, 56.13; H, 6.79; N, 7.70.

³⁰ Found: C, 56.15; H, 6.82; N, 7.53.

¹H-NMR(DMSO-d₆) δ:0.95 (3H, t, J=7.4 Hz), 1.00 (3H, t, J=7.3 Hz), 1.46-1.68 (4H, m), 1.78-1.92 (2H, m), 3.93 (2H, t, J=6.6 Hz), 3.93-4.02 (2H, m), 4.16 (2H, s), 7.66 (1H, dd, J=2.0, 8.4 Hz), 7.72 (1H, d, J=2.0 Hz), 8.28 (1H, d, J=8.4 Hz), 8.75 (3H, bs).

Example 26

- 3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-isobutyl-1(2H)-isoquinolinone hydrochloride
 (1) Ethyl 6,7-dichloro-4-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (1))
 Melting point 111-112°C.
 Elemental analysis for $C_{16}H_{17}NO_4Cl_2$
 Calculated: C, 53.65; H, 4.78; N, 3.91.
 Found: C, 53.62; H, 4.65; N, 3.66.
- (2) Ethyl 4-butoxy-6,7-dichloro-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (2))
 1H -NMR(CDCl₃) δ: 0.90 (6H, d, J=6.8 Hz), 1.01 (3H, t, J=7.4 Hz); 1.44 (3H, t, J=7.1 Hz), 1.48-1.62 (2H, m), 1.72-1.85 (2H, m), 2.05-2.17 (1H, m), 3.88 (2H, d, J=7.6 Hz), 3.94 (2H, t, J=6.5 Hz), 4.46 (2H, q, J=7.1 Hz), 7.81 (1H, s); 8.51 (1H, s).
- (3) 4-Butoxy-6,7-dichloro-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))
 Melting point 104-105°C.
 Elemental analysis for $C_{18}H_{21}NO_4Cl_2$
 Calculated: C, 55.97; H, 5.48; N, 3.63.
 Found: C, 55.82; H, 5.43; N, 3.46.
 1H -NMR(CDCl₃) δ: 0.91 (6H, d, J=6.6 Hz), 1.00 (3H, t, J=7.3 Hz), 1.45-1.64 (2H, m), 1.75-1.86 (2H, m), 2.08-2.22 (1H, m), 3.97-4.05 (4H, m), 7.65 (1H, s), 8.45 (1H, s).
- (4) 4-Butoxy-6,7-dichloro-3-hydroxymethyl-2-isobutyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))
 Melting point 99-100°C.

Elemental analysis for $C_{18}H_{23}NO_3Cl_2$

Calculated: C, 58.07; H, 6.23; N, 3.76.

Found: C, 57.90; H, 6.09; N, 3.46.

¹H-NMR(CDCl₃) δ: 0.92 (6H, d, J=6.6 Hz), 1.05 (3H, t, J=7.3 Hz), 1.50-1.69 (2H, m), 1.80-1.94 (2H, m), 2.04-2.21 (1H, m), 2.57 (1H, bs), 3.88 (2H, t, J=6.6 Hz), 4.09 (2H, d, J=7.8 Hz), 4.79 (2H, d, J=4.8 Hz), 7.69 (1H, d, J=2.0 Hz), 8.35 (1H, d, J=2.0 Hz).

(5) 4-Butoxy-3-chloromethyl-6,7-dichloro-2-isobutyl-
¹⁰ 1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))
¹H-NMR(CDCl₃) δ: 0.95 (6H, d, J=7.0 Hz), 1.05 (3H, t, J=7.3 Hz), 1.51-1.66 (2H, m), 1.82-1.96 (2H, m), 2.04-2.21 (1H, m), 3.97 (2H, t, J=6.5 Hz), 4.06 (2H, d, J=5:8 Hz), 4.77 (2H, s), 7.81 (1H, s), 8.50 (1H, s).
¹⁵ (6) 2-{(4-Butoxy-6,7-dichloro-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl}-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

²⁰ Melting point 103-104°C.

Elemental analysis for $C_{26}H_{26}N_2O_4Cl_2$

Calculated: C, 62.28; H, 5.23; N, 5.59.

Found: C, 62.18; H, 5.03; N, 5.53.

¹H-NMR(CDCl₃) δ: 0.95 (6H, d, J=6.6 Hz), 1.00 (3H, t, J=7.4 Hz), 1.43-1.58 (2H, m), 1.79-1.92 (2H, m), 2.07-2.21 (1H, m), 3.94-4.04 (4H, m), 5.01 (2H, s), 7.70-7.90 (5H, m), 8.49 (1H, s).

(7) Tert-butyl (4-butoxy-6,7-dichloro-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized
³⁰ according to the method similar to that in Example 1 (6))

Melting point 138-139°C.

Elemental analysis for $C_{23}H_{32}N_2O_4Cl_2$

Calculated: C, 58.85; H, 6.44; N, 5.97.

³⁵ Found: C, 58.60; H, 6.64; N, 5.72.

¹H-NMR(CDCl₃) δ: 0.95 (6H, d, J=6.6 Hz), 1.04 (3H, t,

$J=7.3$ Hz), 1.47 (9H, s), 1.47-1.67 (2H, m), 1.79-1.93 (2H, m), 2.07-2.21 (1H, m), 3.84 (2H, t, $J=6.5$ Hz), 3.98 (2H, d, $J=7.4$ Hz), 4.49 (2H, d, $J=5.4$ Hz), 4.80 (1H, bs), 7.75 (1H, s), 8.45 (1H, s).

- ⁵ (8) 3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-isobutyl-1(2H)-isoquinoline hydrochloride (synthesized according to the method similar to that in Example 1 (7))
Melting point 168-170°C.

Elemental analysis for $C_{18}H_{25}N_2O_2Cl_3$

¹⁰ Calculated: C, 53.02; H, 6.18; N, 6.87.

Found: C, 53.28; H, 6.13; N, 6.76.

¹H-NMR(DMSO-d₆) δ : 0.88 (6H, d, $J=6.6$ Hz), 1.00 (3H, t, $J=7.1$ Hz), 1.45-1.63 (2H, m), 1.78-1.96 (2H, m), 1.99-2.09 (1H, m), 3.91-3.99 (4H, m), 4.17 (2H, s), 7.92 (1H, s), 8.38 (1H, s), 8.68 (3H, bs).

Example 27

3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-neopentyl-1(2H)-isoquinolinone hydrochloride

- ²⁰ (1) Ethyl 6,7-dichloro-4-hydroxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (1))
Melting point 117-118°C.

Elemental analysis for $C_{17}H_{19}NO_4Cl_2$

Calculated: C, 54.85; H, 5.14; N, 3.76.

²⁵ Found: C, 54.89; H, 5.14; N, 3.62.

¹H-NMR(CDCl₃) δ : 0.84 (9H, s), 1.47 (3H, t, $J=7.1$ Hz), 4.49 (2H, q, $J=7.1$ Hz), 4.51 (2H, bs), 8.22 (1H, s), 8.52 (1H, s), 10.73 (1H, s).

- ³⁰ (2) Ethyl 4-butoxy-6,7-dichloro-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (2))

¹H-NMR(CDCl₃) δ : 0.93 (9H, s), 1.02 (3H, t, $J=7.3$ Hz), 1.44 (3H, t, $J=7.1$ Hz), 1.48-1.59 (2H, m), 1.73-1.83 (2H, m), 3.94 (2H, t, $J=6.6$ Hz), 4.07 (2H, bs), 4.43 (2H, q, $J=7.1$ Hz), 7.83 (1H, s), 8.51 (1H, s).

(3) 4-Butoxy-6,7-dichloro-2-neopentyl-1-oxo-1,2-dihydro-

3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))

Melting point 138-139°C.

Elemental analysis for $C_{19}H_{23}NO_4Cl_2$

5 Calculated: C, 57.01; H, 5.79; N, 3.50.

Found: C, 57.03; H, 5.86; N, 3.30.

1H -NMR(CDCl₃) δ: 0.93 (9H, s), 1.01 (3H, t, J=7.1 Hz), 1.40-1.64 (2H, m), 1.77-1.91 (2H, m), 4.00 (2H, t, J=6.6 Hz), 4.23 (2H, bs), 5.81 (1H, bs), 7.77 (1H, s), 8.45

10 (1H, s).

(4) 4-Butoxy-6,7-dichloro-3-hydroxymethyl-2-neopentyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))

Melting point 178-179°C.

15 Elemental analysis for $C_{19}H_{25}NO_3Cl_2$

Calculated: C, 59.07; H, 6.52; N, 3.63.

Found: C, 59.00; H, 6.39; N, 3.33.

1H -NMR(CDCl₃) δ: 0.93 (9H, s), 1.06 (3H, t, J=7.3 Hz), 1.56-1.67 (2H, m), 1.81-1.92 (2H, m), 3.08 (1H, t, J=5.9 Hz), 3.90 (2H, t, J=6.4 Hz), 4.20 (2H, bs), 4.84 (2H, bs), 7.66 (1H, s), 8.22 (1H, s).

(5) 4-Butoxy-3-chloromethyl-6,7-dichloro-2-neopentyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

25 1H -NMR(CDCl₃) δ: 0.98 (9H, s), 1.05 (3H, t, J=7.3 Hz), 1.55-1.70 (2H, m), 1.82-1.95 (2H, m), 3.93 (2H, t, J=6.6 Hz), 4.17 (2H, bs), 4.84 (2H, bs), 7.80 (1H, s), 8.50 (1H, s).

(6) 2-{(4-Butoxy-6,7-dichloro-2-neopentyl-1-oxo-1,2-

30 dihydro-3-isoquinolinyl)methyl}-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

Melting point 145-146°C.

Elemental analysis for $C_{27}H_{28}N_2O_4Cl_2$

35 Calculated: C, 62.92; H, 5.48; N, 5.43.

Found: C, 62.76; H, 5.76; N, 5.22.

¹H-NMR(CDCl₃) δ: 1.00 (9H, s), 1.01 (3H, t, J=7.1 Hz), 1.49-1.61 (2H, m), 1.81-1.95 (2H, m), 4.00 (2H, t, J=6.8 Hz), 4.07 (2H, bs), 5.05 (2H, s), 7.70-7.86 (5H, m), 8.47 (1H, s).

- ⁵ (7) Tert-butyl (4-butoxy-6,7-dichloro-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 1 (6))

Melting point 152-153°C.

- ¹⁰ Elemental analysis for C₂₄H₃₄N₂O₄Cl₂

Calculated: C, 59.39; H, 7.06; N, 5.77.

Found: C, 59.15; H, 7.10; N, 5.54.

¹H-NMR(CDCl₃) δ: 0.98 (9H, s), 1.01 (3H, t, J=7.0 Hz),

1.46 (9H, s), 1.53-1.68 (2H, m), 1.80-1.94 (2H, m), 3.85

- ¹⁵ (2H, t, J=6.6 Hz), 4.11-4.28 (2H, m), 4.55 (2H, d, J=5.4 Hz), 4.83 (1H, bs), 7.74 (1H, d, J=1.7 Hz), 8.41 (1H, d, J=1.7 Hz).

(8) 3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-neopentyl-1(2H)-isoquinolinone hydrochloride (synthesized

- ²⁰ according to the method similar to that in Example 1 (7))

Melting point 157-158°C.

Elemental analysis for C₁₉H₂₇N₂O₂Cl₃ 1/2H₂O

Calculated: C, 52.97; H, 6.55; N, 6.50.

- ²⁵ Found: C, 53.04; H, 6.59; N, 6.46.

¹H-NMR(DMSO-d₆) δ: 0.91 (9H, s), 0.99 (3H, t, J=7.1 Hz), 1.45-1.60 (2H, m), 1.77-1.91 (2H, m), 3.95 (2H, t, J=6.4 Hz), 4.11 (2H, bs), 4.24 (2H, bs), 7.92 (1H, s), 8.38 (1H, s), 8.62 (3H, bs).

³⁰ Example 28

3-(Aminomethyl)-2-benzyl-4-butoxy-6,7-dichloro-1(2H)-isoquinolinone hydrochloride

(1) Ethyl 2-benzyl-6,7-dichloro-4-hydroxy-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according

- ³⁵ to the method similar to that in Example 1 (1))

Melting point 140-141°C.

Elemental analysis for $C_{19}H_{15}NO_4Cl_2$

Calculated: C, 58.18; H, 3.85; N, 3.57.

Found: C, 58.22; H, 3.98; N, 3.27.

1H -NMR(CDCl₃) δ : 1.18 (3H, t, J=7.2 Hz), 4.28 (2H, q,

5 J=7.2 Hz), 5.60 (2H, s), 7.03-7.07 (2H, m), 7.20-7.32 (3H, m), 8.26 (1H, s), 8.57 (1H, s), 11.20 (1H, s).

(2) Ethyl 2-benzyl-4-butoxy-6,7-dichloro-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (2))

10 1H -NMR(CDCl₃) δ : 0.98 (3H, t, J=7.3 Hz), 1.13 (3H, t, J=7.2 Hz), 1.40-1.59 (2H, m), 1.70-1.83 (2H, m), 3.92 (2H, t, J=6.4 Hz), 4.17 (2H, q, J=7.2 Hz), 5.34 (2H, s), 7.16-7.31 (5H, m), 7.83 (1H, s), 8.56 (1H, s).

(3) 2-Benzyl-4-butoxy-6,7-dichloro-1-oxo-1,2-dihydro-3-

15 isoquinolinic acid (synthesized according to the method similar to that in Example 4 (3))

Melting point 128-129°C.

Elemental analysis for $C_{21}H_{19}NO_4Cl_2$

Calculated: C, 60.01; H, 4.59; N, 3.33.

20 Found: C, 60.00; H, 4.40; N, 3.11..

1H -NMR(CDCl₃) δ : 0.97 (3H, t, J=7.3 Hz), 1.41-1.60 (2H, m), 1.72-1.86 (2H, m), 3.97 (2H, t, J=6.4 Hz), 4.83 (1H, bs), 5.42 (2H, s), 7.18-7.26 (5H, m), 7.83 (1H, s), 8.53 (1H, s).

25 (4) 2-Benzyl-4-butoxy-6,7-dichloro-3-hydroxymethyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))

Melting point 110-111°C.

Elemental analysis for $C_{21}H_{21}NO_3Cl_2$

30 Calculated: C, 62.08; H, 5.21; N, 3.45.

Found: C, 62.01; H, 5.28; N, 3.25.

1H -NMR(CDCl₃) δ : 1.02 (3H, t, J=7.1 Hz), 1.47-1.65 (2H, m), 1.77-1.91 (2H, m), 2.23 (1H, bs), 3.87 (2H, t, J=6.6 Hz), 4.65 (2H, d, J=5.6 Hz), 5.59 (2H, s), 7.12-7.16 (2H, m), 7.25-7.34 (3H, m), 7.78 (1H, d, J=1.7 Hz), 8.50 (1H, d, J=1.7 Hz).

(5) 2-Benzyl-4-butoxy-3-chloromethyl-6,7-dichloro-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

¹H-NMR(CDCl₃) δ: 1.03 (3H, d, J=7.2 Hz), 1.53-1.64 (2H, m), 1.80-1.95 (2H, m), 4.00 (2H, t, J=6.4 Hz), 4.60 (2H, s), 5.60 (2H, s), 7.10-7.34 (5H, m), 7.85 (1H, s), 8.58 (1H, s).

(6) 2-{(2-Benzyl-4-butoxy-6,7-dichloro-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl}-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

Melting point 161-162°C.

Elemental analysis for C₂₉H₂₈N₂O₄Cl₂

Calculated: C, 65.05; H, 4.52; N, 5.23.

Found: C, 64.98; H, 4.64; N, 5.07.

¹H-NMR(CDCl₃) δ: 1.01 (3H, t, J=7.3 Hz), 1.47-1.65 (2H, m), 1.80-1.94 (2H, m), 4.12 (2H, t, J=6.7 Hz), 5.02 (2H, s), 5.37 (2H, s), 6.65-6.72 (1H, m), 6.78-6.92 (4H, m), 7.51-7.60 (4H, m), 7.90 (1H, s), 8.53 (1H, s).

(7) Tert-butyl (2-benzyl-4-butoxy-6,7-dichloro-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 1 (6))

Melting point 151-152°C.

Elemental analysis for C₂₆H₃₀N₂O₄Cl₂

Calculated: C, 61.78; H, 5.98; N, 5.54.

Found: C, 61.73; H, 6.17; N, 5.45.

¹H-NMR(CDCl₃) δ: 1.02 (3H, t, J=7.3 Hz), 1.42 (9H, s), 1.47-1.60 (2H, m), 1.76-1.87 (2H, m), 3.83 (2H, t, J=6.6 Hz), 4.38 (2H, d, J=6.0 Hz), 4.74 (1H, bs), 5.45 (2H, s), 7.19-7.35 (5H, m), 7.78 (1H, s), 8.53 (1H, s).

(8) 3-(Aminomethyl)-2-benzyl-4-butoxy-6,7-dichloro-1(2H)-isoquinoline hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 191-192°C.

Elemental analysis for C₂₁H₂₃N₂O₂Cl₃

Calculated: C, 57.09; H, 5.25; N, 6.34.

Found: C, 56.77; H, 5.14; N, 6.04.

¹H-NMR(DMSO-d₆) δ:0.97 (3H, t, J=7.3 Hz), 1.43-1.59 (2H, m), 1.76-1.90 (2H, m), 3.91-3.98 (4H, m), 5.47 (2H, s),

⁵ 7.18-7.22 (2H, m), 7.28-7.39 (3H, m), 7.96 (1H, s), 8.43 (1H, s), 8.89 (3H, bs).

Example 29

3-(Aminomethyl)-6,7-dichloro-2-isobutyl-4-pentyloxy-1(2H)-isoquinolinone hydrochloride

¹⁰ (1) Ethyl 6,7-dichloro-2-isobutyl-1-oxo-4-pentyloxy-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (2))

¹H-NMR(CDCl₃) δ:0.90 (6H, d, J=6.6 Hz), 0.96 (3H, t, J=6.6 Hz), 1.29-1.54 (7H, m), 1.74-1.87 (2H, m), 2.05-

¹⁵ 2.17 (1H, m), 3.90 (2H, d, J=5.8 Hz), 3.93 (2H, t, J=6.6 Hz), 4.46 (2H, q, J=7.1 Hz), 7.81 (1H, s), 8.51 (1H, s).

(2) 6,7-Dichloro-2-isobutyl-1-oxo-4-pentyloxy-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4

²⁰ (3))

Melting point 124-125°C.

Elemental analysis for C₁₉H₂₃NO₄Cl₂

Calculated: C, 57.01; H, 5.79; N, 3.50.

Found: C, 57.13; H, 5.72; N, 3.40.

²⁵ ¹H-NMR(CDCl₃) δ:0.90 (6H, d, J=6.6 Hz), 0.95 (3H, t, J=6.6 Hz), 1.31-1.57 (4H, m), 1.77-1.91 (2H, m), 2.07-2.21 (1H, m), 3.95-4.04 (4H, m), 4.35 (1H, bs), 7.75 (1H, s), 8.45 (1H, s).

(3) 6,7-Dichloro-3-hydroxymethyl-2-isobutyl-4-pentyloxy-

³⁰ 1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))

Melting point 86-87°C.

Elemental analysis for C₁₉H₂₅NO₃Cl₂

Calculated: C, 59.07; H, 6.52; N, 3.63.

³⁵ Found: C, 58.91; H, 6.65; N, 3.48.

¹H-NMR(CDCl₃) δ:0.82 (6H, d, J=6.6 Hz), 0.99 (3H, t,

$J=7.0$ Hz), 1.39-1.59 (4H, m), 1.82-1.92 (2H, m), 2.07-2.17 (1H, m), 2.67 (1H, bs), 3.87 (2H, t, $J=6.4$ Hz), 4.09 (2H, d, $J=7.6$ Hz), 4.78 (2H, d, $J=4.8$ Hz), 7.69 (1H, s), 8.35 (1H, s).

5 (4) 3-Chloromethyl-6,7-dichloro-2-isobutyl-4-pentyloxy-1(2H)-isoquinoline (synthesized according to the method similar to that in Example 4 (5))

$^1\text{H-NMR}(\text{CDCl}_3)$ δ : 0.96 (6H, d, $J=6.6$ Hz), 0.99 (3H, t, $J=7.0$ Hz), 1.36-1.61 (4H, m), 1.84-1.98 (2H, m), 2.05-2.22 (1H, m), 3.96 (2H, t, $J=6.4$ Hz), 4.07 (2H, d, $J=7.6$ Hz), 4.78 (2H, s), 7.81 (1H, s), 8.51 (1H, s).

(5) 2-{{(6,7-Dichloro-2-isobutyl-1-oxo-4-pentyloxy-1,2-dihydro-3-isoquinolinyl)methyl}-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to

15 that in Example 4 (6))

Melting point 119-120°C.

Elemental analysis for $\text{C}_{27}\text{H}_{28}\text{N}_2\text{O}_4\text{Cl}_2$

Calculated: C, 62.92; H, 5.48; N, 5.43.

Found: C, 62.95; H, 5.43; N, 5.55.

20 $^1\text{H-NMR}(\text{CDCl}_3)$ δ : 0.88-1.04 (9H, m), 1.30-1.54 (4H, m), 1.80-1.90 (2H, m), 2.05-2.17 (1H, m), 3.90-4.05 (4H, m), 5.06 (2H, s), 7.70-7.89 (5H, m), 8.49 (1H, s).

(6) Tert-butyl (6,7-dichloro-2-isobutyl-1-oxo-4-pentyloxy-1,2-dihydro-3-isoquinolinyl)methylcarbamate

25 (synthesized according to the method similar to that in Example 1 (6))

Melting point 113-114°C.

Elemental analysis for $\text{C}_{24}\text{H}_{34}\text{N}_2\text{O}_4\text{Cl}_2$

Calculated: C, 59.39; H, 7.06; N, 5.77.

30 Found: C, 59.39; H, 7.00; N, 5.67.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ : 0.95 (6H, d, $J=6.6$ Hz), 0.98 (3H, t, $J=7.1$ Hz), 1.38-1.57 (13H, m), 1.81-1.95 (2H, m), 2.07-2.21 (1H, m), 3.84 (2H, t, $J=6.6$ Hz), 3.97 (2H, d, $J=7.4$ Hz), 4.49 (2H, d, $J=5.4$ Hz), 4.81 (1H, bs), 7.75 (1H, s), 8.46 (1H, s).

35 (7) 3-(Aminomethyl)-6,7-dichloro-2-isobutyl-4-pentyloxy-

1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 167-169°C.

⁵ Elemental analysis for C₁₉H₂₇N₂O₂Cl₃

Calculated: C, 54.10; H, 6.45; N, 6.64.

Found: C, 54.09; H, 6.45; N, 6.54.

¹H-NMR(DMSO-d₆) δ:0.88 (6H, d, J=7.0 Hz), 0.95 (3H, t, J=7.0 Hz), 1.31-1.57 (4H, m), 1.80-2.10 (3H, m), 3.91-¹⁰ 3.99 (4H, m), 4.17 (2H, s), 7.92 (1H, s), 8.38 (1H, s), 8.72 (3H, bs).

Example 30

3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-isopropyl-1(2H)-isoquinolinone hydrochloride

¹⁵ (1) Ethyl 6,7-dichloro-4-hydroxy-2-isopropyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (1))

Melting point 124-125°C.

Elemental analysis for C₁₅H₁₅NO₄Cl₂·1/2H₂O

²⁰ Calculated: C, 51.01; H, 4.57; N, 3.97.

Found: C, 51.23; H, 4.25; N, 3.86.

¹H-NMR(CDCl₃) δ:1.45 (3H, t, J=7.1 Hz), 1.62 (6H, d, J=6.6 Hz), 4.19-4.33 (1H, m), 4.47 (2H, q, J=7.1 Hz), 8.17 (1H, s), 8.46 (1H, s), 10.64 (1H, s).

²⁵ (2) Ethyl 4-butoxy-6,7-dichloro-2-isopropyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (2))

¹H-NMR(CDCl₃) δ:1.01 (3H, t, J=7.1 Hz), 1.44 (3H, t, J=7.2 Hz), 1.46-1.59 (2H, m), 1.64 (6H, d, J=6.6 Hz),

³⁰ 1.71-1.85 (2H, m), 3.93 (2H, t, J=6.4 Hz), 4.01-4.18 (1H, m), 4.45 (2H, q, J=7.2 Hz), 7.77 (1H, s), 8.47 (1H, s).

(3) 4-Butoxy-6,7-dichloro-2-isopropyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))

³⁵ Melting point 186-187°C.

Elemental analysis for C₁₇H₁₉NO₄Cl₂

Calculated: C, 54.85; H, 5.14; N, 3.76.

Found: C, 54.90; H, 5.12; N, 3.68.

¹H-NMR(CDCl₃) δ: 0.99 (3H, t, J=7.3 Hz), 1.44-1.62 (2H, m), 1.68 (6H, d, J=6.6 Hz), 1.74-1.88 (2H, m), 4.00 (2H, 5 t, J=6.4 Hz), 4.21-4.34 (1H, m), 5.11 (1H, bs), 7.80 (1H, s), 8.51 (1H, s).

(4) 4-Butoxy-6,7-dichloro-3-hydroxymethyl-2-isopropyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))

10 Melting point 150-151°C.

Elemental analysis for C₁₇H₂₁NO₃Cl₂ 1/4H₂O

Calculated: C, 56.29; H, 5.97; N, 3.86.

Found: C, 56.53; H, 6.01; N, 3.96.

¹H-NMR(CDCl₃) δ: 1.03 (3H, t, J=7.4 Hz), 1.44-1.66 (2H, 15 m), 1.67 (6H, d, J=7.0 Hz), 1.78-1.92 (2H, m), 2.04 (1H, bs), 3.85 (2H, t, J=6.6 Hz), 4.64-4.74 (1H, m), 4.81 (2H, s), 7.73 (1H, s), 8.44 (1H, s).

(5) 4-Butoxy-3-chloromethyl-6,7-dichloro-2-isopropyl-1(2H)-isoquinolinone (synthesized according to the 20 method similar to that in Example 4 (5))

¹H-NMR(CDCl₃) δ: 1.05 (3H, t, J=7.1 Hz), 1.51-1.66 (2H, m), 1.70 (6H, d, J=6.6 Hz), 1.78-1.95 (2H, m), 3.96 (2H, t, J=6.4 Hz), 4.47-4.60 (1H, m), 4.77 (2H, s), 7.77 (1H, s), 8.46 (1H, s).

25 (6) 2-[(4-Butoxy-6,7-dichloro-2-isopropyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl]-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

Melting point 185-186°C.

30 Elemental analysis for C₂₅H₂₄N₂O₄Cl₂

Calculated: C, 61.61; H, 4.96; N, 5.75.

Found: C, 61.71; H, 4.89; N, 5.66.

¹H-NMR(CDCl₃) δ: 1.01 (3H, t, J=7.4 Hz), 1.47 (6H, d, J=6.6 Hz), 1.48-1.68 (2H, m), 1.80-1.94 (2H, m), 4.05

35 (2H, t, J=6.6 Hz), 4.19-4.32 (1H, m), 5.09 (2H, s), 7.73-7.89 (5H, m), 8.43 (1H, s).

(7) Tert-butyl (4-butoxy-6,7-dichloro-2-isopropyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 1 (6))

⁵ Melting point 169.5-170°C.

Elemental analysis for C₂₂H₃₀N₂O₄Cl₂

Calculated: C, 57.77; H, 6.61; N, 6.12.

Found: C, 57.74; H, 6.76; N, 6.13.

¹H-NMR(CDCl₃) δ: 1.03 (3H, t, J=7.4 Hz), 1.47 (9H, s),

¹⁰ 1.48-1.62 (2H, m), 1.63 (6H, d, J=6.6 Hz), 1.71-1.92 (2H, m), 3.81 (2H, t, J=6.4 Hz), 4.41-4.52 (1H, m), 4.53 (2H, d, J=5.4 Hz), 4.67 (1H, bs), 7.73 (1H, s), 8.45 (1H, s).

(8) 3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-isopropyl-1(2H)-isoquinolinone hydrochloride (synthesized

¹⁵ according to the method similar to that in Example 1 (7))

Melting point 264-265°C.

Elemental analysis for C₁₇H₂₃N₂O₂Cl₃

Calculated: C, 51.86; H, 5.89; N, 7.11.

²⁰ Found: C, 52.00; H, 5.70; N, 7.18.

¹H-NMR(DMSO-d₆) δ: 0.99 (3H, t, J=7.1 Hz), 1.45-1.56 (2H, m), 1.57 (6H, d, J=6.6 Hz), 1.77-1.91 (2H, m), 3.90 (2H, t, J=6.4 Hz), 4.23 (2H, s), 4.36-4.49 (1H, m), 7.87 (1H, s), 8.34 (1H, s), 8.85 (3H, bs).

²⁵ Example 31

3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-cyclopropyl-1(2H)-isoquinolinone hydrochloride

(1) Ethyl 2-cyclopropyl-6,7-dichloro-4-hydroxy-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized

³⁰ according to the method similar to that in Example 1 (1))

Melting point 119.5-120°C.

Elemental analysis for C₁₅H₁₃NO₄Cl₂

Calculated: C, 52.63; H, 3.83; N, 4.09.

³⁵ Found: C, 52.97; H, 3.90; N, 3.78.

¹H-NMR(CDCl₃) δ: 0.62-0.70 (2H, m), 1.05-1.16 (2H, m),

- 1.44 (3H, t, J=7.2 Hz), 3.33-3.44 (1H, m), 4.48 (2H, q, J=7.2 Hz), 8.16 (1H, s), 8.47 (1H, s), 10.58 (1H, s).
(2) Ethyl 4-butoxy-6,7-dichloro-2-cyclopropyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according
5 to the method similar to that in Example 1 (2))
Melting point 72.5-73.5°C.
Elemental analysis for $C_{19}H_{21}NO_4Cl_2$
Calculated: C, 57.30; H, 5.31; N, 3.52.
Found: C, 57.24; H, 5.24; N, 3.47.
10 1H -NMR(CDCl₃) δ: 0.82-0.91 (2H, m), 1.01 (3H, t, J=7.3 Hz), 1.01-1.15 (2H, m), 1.44 (3H, t, J=7.2 Hz), 1.43-1.60 (2H, m), 1.72-1.86 (2H, m), 3.10-3.22 (1H, m), 3.94 (2H, t, J=6.5 Hz), 4.46 (2H, q, J=7.2 Hz), 7.80 (1H, s), 8.47 (1H, s).
15 (3) 4-Butoxy-6,7-dichloro-2-cyclopropyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))
Melting point 198-201°C.
20 Elemental analysis for $C_{17}H_{17}NO_4Cl_2$
Calculated: C, 55.15; H, 4.68; N, 3.78.
Found: C, 55.14; H, 4.47; N, 3.73.
 1H -NMR(CDCl₃) δ: 0.85-0.94 (2H, m), 1.00 (3H, t, J=7.3 Hz), 1.14-1.30 (2H, m), 1.42-1.63 (2H, m), 1.75-1.89 (2H, m), 3.26-3.35 (1H, m), 4.00 (2H, t, J=6.4 Hz), 5.55 (1H, bs), 7.75 (1H, s), 8.41 (1H, s).
(4) 4-Butoxy-6,7-dichloro-2-cyclopropyl-3-hydroxymethyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))
30 Melting point 145-146°C.
Elemental analysis for $C_{17}H_{19}NO_3Cl_2$
Calculated: C, 57.32; H, 5.38; N, 3.93.
Found: C, 57.28; H, 5.17; N, 3.97.
 1H -NMR(CDCl₃) δ: 0.82-0.91 (2H, m), 1.06 (3H, t, J=7.2 Hz), 1.21-1.32 (2H, m), 1.51-1.70 (2H, m), 1.80-1.94 (2H, m), 3.04 (1H, bs), 3.13-3.22 (1H, m), 3.90 (2H, t, J=6.4

Hz), 4.98 (2H, d, J=5.8 Hz), 7.65 (1H, s), 8.25 (1H, s).
 (5) 4-Butoxy-3-chloromethyl-6,7-dichloro-2-cyclopropyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

5 $^1\text{H-NMR}(\text{CDCl}_3)$ δ : 0.87-0.95 (2H, m), 1.04 (3H, t, J=7.4 Hz), 1.22-1.37 (2H, m), 1.50-1.69 (2H, m), 1.80-1.95 (2H, m), 3.14-3.25 (1H, m), 3.93 (2H, t, J=6.6 Hz), 5.03 (2H, s), 7.76 (1H, s), 8.45 (1H, s).

(6) 2-(4-Butoxy-6,7-dichloro-2-cyclopropyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

Melting point 197-198°C.

Elemental analysis for $\text{C}_{25}\text{H}_{22}\text{N}_2\text{O}_4\text{Cl}_2$

15 Calculated: C, 61.87; H, 4.57; N, 5.77.

Found: C, 61.93; H, 4.50; N, 5.84.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ : 0.82-0.91 (2H, m), 1.00 (3H, t, J=7.3 Hz), 1.26-1.37 (2H, m), 1.43-1.61 (2H, m), 1.75-1.90 (2H, m), 2.84-2.95 (1H, m), 3.98 (2H, t, J=6.8 Hz), 5.25 (2H, s), 7.69-7.84 (5H, m), 8.42 (1H, s).

(7) Tert-butyl (4-butoxy-6,7-dichloro-2-cyclopropyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 1 (6))

25 Melting point 143-144°C.

Elemental analysis for $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_4\text{Cl}_2$

Calculated: C, 58.03; H, 6.20; N, 6.15.

Found: C, 58.09; H, 6.33; N, 5.95.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ : 0.79-0.88 (2H, m), 1.04 (3H, t, J=7.3 Hz), 1.25-1.39 (2H, m), 1.44 (9H, s), 1.48-1.67 (2H, m), 1.76-1.93 (2H, m), 2.97-3.08 (1H, m), 3.86 (2H, t, J=6.6 Hz), 4.73 (2H, d, J=5.6 Hz), 4.95 (1H, bs), 7.71 (1H, s), 8.38 (1H, s).

(8) 3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-cyclopropyl-1(2H)-isoquinoline hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 238°C.

Elemental analysis for C₁₇H₂₁N₂O₂Cl₃

Calculated: C, 52.12; H, 5.40; N, 7.15.

Found: C, 51.96; H, 5.30; N, 6.99.

⁵ ¹H-NMR(DMSO-d₆) δ:0.84-0.92 (2H, m), 0.99 (3H, t, J=7.3 Hz), 1.19-1.30 (2H, m), 1.44-1.63 (2H, m), 1.77-1.91 (2H, m), 3.13-3.21 (1H, m), 3.93 (2H, t, J=6.0 Hz), 4.38 (2H, bs), 7.85 (1H, s), 8.30 (1H, s), 8.78 (3H, bs).

Example 32

¹⁰ 3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-cyclopropylmethyl-1(2H)-isoquinoline hydrochloride
(1) Ethyl 6,7-dichloro-2-cyclopropylmethyl-4-hydroxy-1-oxo-1,2-dihydro-3-isooquinolinecarboxylate (synthesized according to the method similar to that in Example 1

¹⁵ (1))
Melting point 109.5-110°C.
Elemental analysis for C₁₆H₁₅NO₄Cl₂
Calculated: C, 53.95; H, 4.24; N, 3.93.
Found: C, 54.03; H, 4.04; N, 3.95.
²⁰ ¹H-NMR(CDCl₃) δ:0.32-0.54 (4H, m), 0.96-1.16 (1H, m), 1.48 (3H, t, J=7.2 Hz), 4.33 (2H, d, J=6.8 Hz), 4.52 (2H, q, J=7.2 Hz), 8.23 (1H, s), 8.51 (1H, s), 11.17 (1H, s).
(2) Ethyl 4-butoxy-6,7-dichloro-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isooquinolinecarboxylate (synthesized

²⁵ according to the method similar to that in Example 1
(2))
¹H-NMR(CDCl₃) δ:0.38-0.57 (4H, m), 1.01 (3H, t, J=7.4 Hz), 1.16-1.26 (1H, m), 1.45 (3H, t, J=7.4 Hz), 1.47-1.62 (2H, m), 1.68-1.86 (2H, m), 3.89-3.99 (4H, m), 4.47 (2H, q, J=7.4 Hz), 7.81 (1H, s), 8.51 (1H, s).
(3) 4-Butoxy-6,7-dichloro-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isooquinolinic acid (synthesized according to the method similar to that in Example 4
(3))

³⁵ Melting point 150-151°C.

Elemental analysis for C₁₈H₁₉NO₄Cl₂

Calculated: C, 56.26; H, 4.98; N, 3.65.

Found: C, 56.45; H, 5.02; N, 3.67.

¹H-NMR(CDCl₃) δ:0.41-0.58 (4H, m), 1.00 (3H, t, J=7.3 Hz), 1.20-1.33 (1H, m), 1.45-1.64 (2H, m), 1.76-1.90 (2H, m), 4.01 (2H, t, J=6.5 Hz), 4.06 (2H, d, J=7.4 Hz), 7.74 (1H, s), 8.46 (1H, s).

(4) 4-Butoxy-6,7-dichloro-2-cyclopropylmethyl-3-hydroxymethyl-1(2H)-isoquinoline (synthesized according to the method similar to that in Example 4 (4))

10 Melting point 130-130.5°C.

Elemental analysis for C₁₈H₂₁NO₃Cl₂

Calculated: C, 58.39; H, 5.72; N, 3.78.

Found: C, 58.46; H, 5.84; N, 3.77.

¹H-NMR(CDCl₃) δ:0.46-0.58 (4H, m), 1.04 (3H, t, J=7.4 Hz), 1.08-1.24 (1H, m), 1.50-1.68 (2H, m), 1.79-1.94 (2H, m), 2.33 (1H, bs), 3.88 (2H, t, J=6.8 Hz), 4.19 (2H, d, J=7.0 Hz), 4.83 (2H, d, J=5.6 Hz), 7.72 (1H, s), 8.42 (1H, s).

(5) 4-Butoxy-3-chloromethyl-6,7-dichloro-2-cyclopropylmethyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

¹H-NMR(CDCl₃) δ:0.44-0.62 (4H, m), 1.02-1.15 (4H, m), 1.52-1.71 (2H, m), 1.83-1.97 (2H, m), 3.99 (2H, t, J=6.6 Hz), 4.20 (2H, d, J=6.6 Hz), 4.83 (2H, s), 7.81 (1H, s), 8.51 (1H, s).

(6) 2-(4-Butoxy-6,7-dichloro-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isooquinolinyl)methyl-1H-isoiindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

Melting point 162-163°C.

Elemental analysis for C₂₆H₂₄N₂O₄Cl₂

Calculated: C, 62.53; H, 4.84; N, 5.61.

Found: C, 62.64; H, 4.77; N, 5.61.

¹H-NMR(CDCl₃) δ:0.47-0.50 (4H, m), 0.95-1.08 (4H, m), 1.43-1.62 (2H, m), 1.78-1.92 (2H, m), 3.98 (2H, t, J=6.7

Hz), 4.15 (2H, d, J=6.6 Hz), 5.05 (2H, s), 7.71-7.86 (5H, m), 8.49 (1H, s).

(7) Tert-butyl (4-butoxy-6,7-dichloro-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-

⁵ isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 1 (6))
Melting point 141.5-142.5°C.

Elemental analysis for C₂₃H₃₀N₂O₄Cl₂

Calculated: C, 58.85; H, 6.44; N, 5.97.

¹⁰ Found: C, 58.84; H, 6.32; N, 6.04.

¹H-NMR(CDCl₃) δ: 0.50-0.59 (4H, m), 1.04 (3H, t, J=7.4 Hz), 1.08-1.28 (1H, m), 1.47 (9H, s), 1.53-1.68 (2H, m), 1.80-1.94 (2H, m), 3.86 (2H, t, J=6.4 Hz), 4.08 (2H, d, J=6.6 Hz), 4.52 (2H, d, J=5.8 Hz), 4.87 (1H, bs), 7.74

¹⁵ (1H, s), 8.45 (1H, s).

(8) 3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-cyclopropylmethyl-1(2H)-isoquinoline hydrochloride
(synthesized according to the method similar to that in Example 1 (7))

²⁰ Melting point 227-228°C.

Elemental analysis for C₁₈H₂₃N₂O₂Cl₃

Calculated: C, 53.28; H, 5.71; N, 6.90.

Found: C, 53.18; H, 5.71; N, 6.75.

¹H-NMR(DMSO-d₆) δ: 0.47 (4H, d, J=6.6 Hz), 1.00 (3H, t, J=7.3 Hz), 1.13-1.26 (1H, m), 1.45-1.64 (2H, m), 1.78-1.92 (4H, m), 3.96 (3H, t, J=6.4 Hz), 4.06 (6H, d, J=6.6 Hz), 4.20 (2H, d, J=4.0 Hz), 7.92 (1H, s), 8.39 (1H, s), 8.72 (3H, bs).

Example 33

³⁰ 3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-isopentyl-1(2H)-isoquinolinone hydrochloride

(1) Ethyl 6,7-dichloro-4-hydroxy-2-isopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (1))

³⁵ Melting point 118-120°C.

Elemental analysis for C₁₆H₁₅NO₄Cl₂

Calculated: C, 54.85; H, 5.14; N, 3.76.

Found: C, 54.63; H, 5.03; N, 3.52.

¹H-NMR(CDCl₃) δ: 0.96 (6H, d, J=6.2 Hz), 1.47 (3H, t, J=7.2 Hz), 1.58-1.65 (3H, m), 4.26-4.34 (2H, m), 4.52

⁵ (2H, q, J=7.2 Hz), 8.22 (1H, s), 8.51 (1H, s), 11.24 (1H, s).

(2) Ethyl 4-butoxy-6,7-dichloro-2-isopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (2))

¹⁰ ¹H-NMR(CDCl₃) δ: 0.95 (6H, d, J=6.2 Hz), 1.01 (3H, t, J=7.0 Hz), 1.39-1.86 (10H, m), 3.91-3.98 (4H, m), 4.46 (2H, q, J=7.2 Hz), 7.80 (1H, s), 8.50 (1H, s).

(3). 4-Butoxy-6,7-dichloro-2-isopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to

¹⁵ the method similar to that in Example 4 (3))

Melting point 100-101°C.

Elemental analysis for C₁₉H₂₃NO₄Cl₂

Calculated: C, 57.01; H, 5.79; N, 3.50.

Found: C, 56.83; H, 5.88; N, 3.51.

²⁰ ¹H-NMR(CDCl₃) δ: 0.94-1.03 (98H, m), .45-1.88 (7H, m), 3.99 (2H, t, J=6.4 Hz), 4.04-4.11 (2H, m), 5.59 (1H, bs), 7.76 (1H, s), 8.46 (1H, s).

(4) 4-Butoxy-6,7-dichloro-3-hydroxymethyl-2-isopentyl-1(2H)-isoquinolinone (synthesized according to the

²⁵ method similar to that in Example 4 (4))

Melting point 102-103.5°C.

Elemental analysis for C₁₉H₂₅NO₃Cl₂

Calculated: C, 59.07; H, 6.52; N, 3.63.

Found: C, 58.78; H, 6.64; N, 3.60.

³⁰ ¹H-NMR(CDCl₃) δ: 0.99 (6H, d, J=6.6 Hz), 1.04 (3H, t, J=7.4 Hz), 1.49-1.92 (7H, m), 2.56 (1H, bs), 3.86 (2H, t, J=6.5 Hz), 4.18-4.26 (2H, m), 4.76 (2H, s), 7.69 (1H, s), 8.38 (1H, s).

(5) 4-Butoxy-3-chloromethyl-6,7-dichloro-2-isopentyl-

³⁵ 1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

- ¹H-NMR(CDCl₃) δ:1.01 (6H, d, J=6.2 Hz), 1.05 (3H, t, J=7.3 Hz), 1.52-1.96 (7H, m), 3.98 (2H, t, J=6.4 Hz), 4.10-4.25 (2H, m), 4.75 (2H, s), 7.81 (1H, s), 8.50 (1H, s).
- ⁵ (6) 2-[(4-Butoxy-6,7-dichloro-2-isopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl]-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))
Melting point 115-119°C.
- ¹⁰ Elemental analysis for C₂₇H₂₈N₂O₄Cl₂
Calculated: C, 62.92; H, 5.48; N, 5.43.
Found: C, 63.10; H, 5.30; N, 5.76.
¹H-NMR(CDCl₃) δ:0.85 (6H, d, J=6.4 Hz), 1.00 (3H, t, J=7.2 Hz), 1.38-1.63 (5H, m), 1.78-1.92 (2H, m), 3.99 (2H, t, J=6.8 Hz), 4.07-4.15 (2H, m), 5.02 (2H, s), 7.73-7.90 (5H, m), 8.48 (1H, s).
- ¹⁵ (7) Tert-butyl (4-butoxy-6,7-dichloro-2-isopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 1 (6))
Melting point 129-129.5°C.
- Elemental analysis for C₂₄H₃₄N₂O₄Cl₂
Calculated: C, 59.38; H, 7.06; N, 5.77.
Found: C, 59.48; H, 7.32; N, 5.80.
- ²⁰ ¹H-NMR(CDCl₃) δ:0.99 (6H, d, J=6.6 Hz), 1.04 (3H, t, J=7.3 Hz), 1.47 (9H, s), 1.52-1.69 (4H, m), 1.73-1.93 (3H, m), 3.83 (2H, t, J=6.5 Hz), 4.06-4.14 (2H, m), 4.47 (2H, d, J=6.4 Hz), 4.72 (1H, bs), 7.75 (1H, s), 8.47 (1H, s).
- ²⁵ (8) 3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-isopentyl-1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7))
Melting point 251-253°C.
- ³⁰ Elemental analysis for C₁₉H₂₇N₂O₂Cl₃
Calculated: C, 54.10; H, 6.45; N, 6.64.

Found: C, 54.13; H, 6.44; N, 6.64.

¹H-NMR(DMSO-d₆) δ:0.96 (6H, d, J=6.6 Hz), 1.00 (3H, t, J=7.3 Hz), 1.42-1.92 (7H, m), 3.94 (2H, t, J=6.6 Hz), 4.05-4.13 (4H, m), 7.91 (1H, s), 8.38 (1H, s), 8.79 (3H, bs).

Example 34

3-(Aminomethyl)-6,7-dichloro-4-isobutoxy-2-neopentyl-1(2H)-isoquinolinone hydrochloride

(1) Ethyl 6,7-dichloro-4-isobutoxy-2-neopentyl-1-oxo-
10 1,2-dihydro-3-isoquinolinecarboxylate (synthesized
according to the method similar to that in Example 1
(2))

¹H-NMR(CDCl₃) δ:0.93 (9H, s), 1.08 (6H, d, J=6.6 Hz),
1.43 (3H, t, J=7.1 Hz), 2.04-2.19 (1H, m), 3.70 (2H, d,
J=6.6 Hz), 4.04 (2H, bs), 4.42 (2H, q, J=7.1 Hz), 7.83
(1H, s), 8.51 (1H, s).

(2) 6,7-Dichloro-4-isobutoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized
according to the method similar to that in Example 4
20 (3))

Melting point 156-157°C.

Elemental analysis for C₁₉H₂₃NO₄Cl₂

Calculated: C, 57.01; H, 5.79; N, 3.50..

Found: C, 57.14; H, 5.55; N, 3.58.

¹H-NMR(CDCl₃) δ:0.93 (9H, s), 1.10 (6H, d, J=6.6 Hz),
2.11-2.24 (1H, m), 3.78 (2H, d, J=6.2 Hz), 4.21 (2H, bs),
7.76 (1H, s), 8.43 (1H, s).

(3) 6,7-Dichloro-3-hydroxymethyl-4-isobutoxy-2-neopentyl-1(2H)-isoquinolinone (synthesized according to
30 the method similar to that in Example 4 (4))

Melting point 180-180.5°C.

Elemental analysis for C₁₉H₂₅NO₃Cl₂ 1/2H₂O

Calculated: C, 58.39; H, 6.58; N, 3.58.

Found: C, 58.52; H, 6.68; N, 3.57.

¹H-NMR(CDCl₃) δ:0.94 (9H, s), 1.16 (6H, d, J=6.6 Hz),
2.12-2.29 (1H, m), 3.09 (1H, bs), 3.67 (2H, d, J=6.2 Hz),

4.21 (2H, bs), 4.83 (2H, bs), 7.67-7.68 (1H, m), 8.22-8.26 (1H, m).

(4) 3-Chloromethyl-6,7-dichloro-4-isobutoxy-2-neopentyl-1(2H)-isoquinolinone (synthesized according to the

⁵ method similar to that in Example 4 (5))

¹H-NMR(CDCl₃) δ:0.98 (9H, s), 1.15 (6H, d, J=6.6 Hz), 2.15-2.25 (1H, m), 3.71 (2H, d, J=6.2 Hz), 4.19 (2H, bs), 4.85 (2H, bs), 7.81 (1H, s), 8.50 (1H, s).

(5) 2-(6,7-Dichloro-1-oxo-4-isobutoxy-2-neopentyl-1,2-

¹⁰ dihydro-3-isoquinolinyl)methyl-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

Melting point 147-148°C.

Elemental analysis for C₂₇H₂₆N₂O₄Cl₂

¹⁵ Calculated: C, 62.92; H, 5.48; N, 5.43.

Found: C, 62.85; H, 5.59; N, 5.42.

¹H-NMR(CDCl₃) δ:1.00 (9H, s), 1.11 (6H, d, J=6.6 Hz), 2.17-2.31 (1H, m), 3.76 (2H, d, J=6.6 Hz), 4.03 (2H, bs), 5.05 (2H, s), 7.71-7.84 (5H, m), 8.47 (1H, s).

²⁰ (6) Tert-butyl (6,7-dichloro-4-isobutoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate

(synthesized according to the method similar to that in Example 1 (6))

Melting point 171-172°C.

²⁵ Elemental analysis for C₂₄H₃₄N₂O₄Cl₂

Calculated: C, 59.38; H, 7.06; N, 5.77.

Found: C, 59.49; H, 6.96; N, 5.91.

¹H-NMR(CDCl₃) δ:0.98 (9H, s), 1.13 (6H, d, J=6.6 Hz), 1.46 (9H, s), 2.13-2.27 (1H, m), 3.61 (2H, d, J=6.2 Hz),

³⁰ 4.12 (2H, bs), 4.54 (2H, d, J=5.4 Hz), 4.77 (1H, bs), 7.76 (1H, s), 8.45 (1H, s).

(7) 3-(Aminomethyl)-6,7-dichloro-4-isobutoxy-2-neopentyl-1(2H)-isoquinolinone hydrochloride

(synthesized according to the method similar to that in

³⁵ Example 1 (7))

Melting point 254-256°C.

Elemental analysis for C₁₉H₂₇N₂O₂Cl₃

Calculated: C, 54.10; H, 6.45; N, 6.64.

Found: C, 53.76; H, 6.40; N, 6.47.

- ¹H-NMR(DMSO-d₆) δ:0.91 (9H, s), 1.10 (6H, d, J=6.6 Hz),
⁵ 2.14-2.27 (1H, m), 3.73 (2H, d, J=6.6 Hz), 4.11 (2H, bs),
4.24 (2H, s), 7.89 (1H, s), 8.38 (1H, s), 8.63 (3H, bs).

Example 35

3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-[3-oxo-(1-pyrrolidinyl)propyl]-1(2H)-isoquinolinone hydrochloride

- ¹⁰ (1) tert-butyl 6,7-dichloro-2-(3-ethoxy-3-oxopropyl)-4-hydroxy-1-oxo-1,2-dihydro-3-isooquinolinecarboxylate
(synthesized according to the method similar to that in Example 1 (1))

Melting point 114-115°C.

- ¹⁵ Elemental analysis for C₁₉H₂₁NO₆Cl₂

Calculated: C, 53.04; H, 4.92; N, 3.26.

Found: C, 53.04; H, 4.94; N, 3.16.

- ¹H-NMR(CDCl₃) δ:1.24 (3H, t, J=7.2 Hz), 1.66 (9H, s),
2.86-2.93 (2H, m), 4.15 (2H, q, J=7.2 Hz), 4.39-4.47 (2H,
²⁰ m), 8.22 (1H, s), 8.49 (1H, s), 11.30 (1H, s).
(2) Tert-butyl 4-butoxy-6,7-dichloro-2-(3-ethoxy-3-oxopropyl)-1-oxo-1,2-dihydro-3-isooquinolinecarboxylate.
(synthesized according to the method similar to that in Example 1 (2))

- ²⁵ Melting point 89-90°C.

Elemental analysis for C₂₃H₂₉NO₆Cl₂

Calculated: C, 56.80; H, 6.01; N, 2.88.

Found: C, 56.84; H, 5.93; N, 2.92.

- ¹H-NMR(CDCl₃) δ:1.01 (3H, t, J=7.4 Hz), 1.26 (3H, t,
³⁰ J=7.1 Hz), 1.48-1.61 (2H, m), 1.64 (9H, s), 1.74-1.85 (2H, m), 2.82-2.90 (2H, m), 3.95 (2H, t, J=6.4 Hz),
4.12-4.22 (4H, m), 7.80 (1H, s), 8.48 (1H, s).
(3) A solution of tert-butyl 4-butoxy-6,7-dichloro-2-(3-ethoxy-3-oxopropyl)-1-oxo-1,2-dihydro-3-
³⁵ isooquinolinecarboxylate (2.43 g, 5 mmol) in trifluoroacetic acid (10 ml) was stirred at room

temperature for 2 h. The reaction mixture was concentrated under reduced pressure and the residue was recrystallized from ethyl acetate - diisopropyl ether to give 4-butoxy-6,7-dichloro-2-(3-ethoxy-3-oxopropyl)-1-

⁵ oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (2.06 g, 95.8%) as crystals.

Melting point 117.5-118°C.

Elemental analysis for C₁₉H₂₁NO₆Cl₂

Calculated: C, 53.04; H, 4.92; N, 3.26.

¹⁰ Found: C, 53.20; H, 4.83; N, 3.30.

¹H-NMR(CDCl₃) δ: 1.00 (3H, t, J=7.3 Hz), 1.24 (3H, t, J=7.2 Hz), 1.44-1.63 (2H, m), 1.75-1.89 (2H, m), 2.96 (2H, t, J=7.3 Hz), 4.00 (2H, t, J=6.4 Hz), 4.15 (2H, t, J=7.2 Hz), 4.30 (2H, t, J=7.2 Hz), 5.01 (1H, bs), 7.83

¹⁵ (1H, s), 8.50 (1H, s).

(4) Ethyl 3-[4-butoxy-6,7-dichloro-3-hydroxymethyl-1-oxo-2(1H)-isoquinolinyl]propionate (synthesized according to the method similar to that in Example 4 (4))

²⁰ Melting point 122-123°C.

Elemental analysis for C₁₉H₂₃NO₅Cl₂

Calculated: C, 54.82; H, 5.57; N, 3.36.

Found: C, 54.71; H, 5.51; N, 3.37.

¹H-NMR(CDCl₃) δ: 1.03 (3H, t, J=7.4 Hz), 1.23 (3H, t,

²⁵ J=7.2 Hz), 1.49-1.67 (2H, m), 1.78-1.92 (2H, m), 2.82 (1H, bs), 2.92 (2H, t, J=6.9 Hz), 3.89 (2H, t, J=6.4 Hz), 4.13 (2H, q, J=7.2 Hz), 4.43 (2H, t, J=6.9 Hz), 4.86 (2H, s), 7.78 (1H, s), 8.44 (1H, s).

(5) Ethyl 3-[4-butoxy-3-chloromethyl-6,7-dichloro-1-oxo-

³⁰ 2(1H)-isoquinolinyl]propionate (synthesized according to the method similar to that in Example 4 (5))

¹H-NMR(CDCl₃) δ: 1.05 (3H, t, J=7.1 Hz), 1.22 (3H, t,

J=7.0 Hz), 1.51-1.66 (2H, m), 1.70-1.95 (2H, m), 2.89

(2H, t, J=6.8 Hz), 3.96 (2H, t, J=6.6 Hz), 4.11 (2H, q,

³⁵ J=7.0 Hz), 4.42 (2H, t, J=6.8 Hz), 4.95 (2H, s), 7.81 (1H, s), 8.49 (1H, s).

(6) Ethyl 3-[4-butoxy-6,7-dichloro-3-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-1-oxo-2(1H)-isoquinolinyl]propionate
Melting point 167-169°C.

5 Elemental analysis for $C_{27}H_{26}N_2O_6Cl_2$

Calculated: C, 59.46; H, 4.80; N, 5.14.

Found: C, 59.54; H, 4.66; N, 5.11.

1H -NMR(CDCl₃) δ : 1.00 (3H, t, J=7.1 Hz), 1.19 (3H, t, J=7.1 Hz), 1.47-1.61 (2H, m), 1.78-1.93 (2H, m), 2.77 (2H, t, J=7.0 Hz), 3.97 (2H, t, J=6.7 Hz), 4.07 (2H, q, J=7.1 Hz), 4.39 (2H, t, J=7.0 Hz), 5.13 (2H, s), 7.72-7.87 (5H, m), 8.47 (1H, s).

(7) A mixture of ethyl 3-[4-butoxy-6,7-dichloro-3-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-1-oxo-2(1H)-isoquinolinyl]propionate (1.36 g, 2.5 mmol) in 6N

hydrochloric acid (15 ml) and acetic acid (15 ml) was refluxed with stirring for 2 h. The reaction mixture was concentrated under reduced pressure, and the residue was recrystallized from tetrahydrofuran - diisopropyl

ether to give 3-[4-butoxy-6,7-dichloro-3-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-1-oxo-2(1H)-isoquinolinyl]propionic acid (1.08 g, 83.7%) as crystals.

Melting point 196-197°C.

Elemental analysis for $C_{26}H_{22}N_2O_6Cl_2 \cdot 2H_2O$

25 Calculated: C, 54.26; H, 4.74; N, 5.06.

Found: C, 54.32; H, 4.38; N, 5.13.

1H -NMR(CDCl₃) δ : 0.99 (3H, t, J=7.1 Hz), 1.42-1.60 (2H, m), 1.77-1.91 (2H, m), 2.76 (2H, t, J=7.1 Hz), 3.94 (2H, t, J=6.8 Hz), 4.41 (2H, t, J=7.1 Hz), 5.13 (2H, s),

30 7.73-7.86 (5H, m), 8.44 (1H, s).

(8) A solution of 3-[4-butoxy-6,7-dichloro-3-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-1-oxo-2(1H)-isoquinolinyl]propionic acid (1.03 g, 2.4 mmol), pyrrolidine (0.20 ml, 2.4 mmol), 1-ethyl-3-(3-

35 dimethylaminopropyl)carbodiimide hydrochloride (0.46 g, 2.4 mmol) and 1-hydroxybenzotriazole (0.37 g, 2.4 mmol)

- in N,N-dimethylformamide (10 ml) was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from tetrahydrofuran - diisopropyl ether to give 2-[4-butoxy-6,7-dichloro-1-oxo-2-[3-oxo-3-(1-pyrrolidinyl)propyl]-1,2-dihydro-3-isoquinolinyl]-methyl]-1H-isoindole-1,3(2H)-dione (0.72 g, 66.1%) as crystals.
- Melting point 222-222.5°C.
- Elemental analysis for $C_{29}H_{29}N_3O_5Cl_2$
- Calculated: C, 61.01; H, 5.12; N, 7.37.
- Found: C, 60.91; H, 5.16; N, 7.21.
- 1H -NMR(CDCl₃) δ: 0.98 (3H, t, J=7.1 Hz), 1.41-1.59 (2H, m), 1.74-1.92 (6H, m), 2.78 (2H, t, J=7.0 Hz), 3.25-3.38 (4H, m), 3.94 (2H, t, J=6.8 Hz), 4.46 (2H, t, J=7.0 Hz), 5.23 (2H, s), 7.70-7.85 (5H, m), 8.47 (1H, s).
- (9) Tert-butyl {4-butoxy-6,7-dichloro-1-oxo-{3-oxo-3-(1-pyrrolidinyl)propyl}-1,2-dihydro-3-isoquinolinyl}-methylcarbamate (synthesized according to the method similar to that in Example 1 (6))
- Melting point 215-217°C.
- Elemental analysis for $C_{26}H_{35}N_3O_5Cl_2$
- Calculated: C, 57.78; H, 6.53; N, 7.77.
- Found: C, 57.95; H, 6.43; N, 7.60.
- 1H -NMR(CDCl₃) δ: 1.03 (3H, t, J=7.3 Hz), 1.44 (9H, s), 1.51-1.62 (2H, m), 1.79-1.95 (6H, m), 2.86 (2H, t, J=6.8 Hz), 3.36-3.45 (4H, m), 3.88 (2H, t, J=6.6 Hz), 4.73 (2H, t, J=6.8 Hz), 4.60 (2H, d, J=5.4 Hz), 5.80 (1H, bs), 7.79 (1H, s), 8.45 (1H, s).
- (10) 3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-{3-oxo-(1-pyrrolidinyl)propyl}-1(2H)-isoquinolinone hydrochloride
- (synthesized according to the method similar to that in Example 1 (7))

Melting point 206-206.5°C.

Elemental analysis for $C_{21}H_{28}N_3O_3Cl_3 \cdot 3/2H_2O$

Calculated: C, 50.06; H, 6.20; N, 8.34.

Found: C, 49.72; H, 6.02; N, 8.23.

⁵ 1H -NMR(DMSO-d₆) δ: 0.99 (3H, d, J=7.4 Hz), 1.45-1.63 (2H, m), 1.71-1.88 (6H, m), 2.76 (2H, t, J=6.6 Hz), 3.23-3.38 (4H, m), 3.93 (2H, t, J=6.4 Hz), 4.21-4.28 (4H, m), 7.91 (1H, s), 8.36 (1H, s), 8.79 (3H, bs).

Example 36

¹⁰ 3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-methyl-1(2H)-isoquinolinone hydrochloride

(1) Ethyl 4-butoxy-6,7-dichloro-4-hydroxy-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1

¹⁵ (1))

Melting point 78-80°C.

Elemental analysis for $C_{17}H_{19}NO_6Cl_2 \cdot 1/4H_2O$

Calculated: C, 54.20; H, 5.22; N, 3.72.

Found: C, 54.16; H, 5.06; N, 3.61.

²⁰ 1H -NMR(CDCl₃) δ: 1.01 (3H, t, J=7.1 Hz), 1.44 (3H, t, J=7.2 Hz), 1.47-1.58 (2H, m), 1.72-1.86 (2H, m), 3.51 (3H, s), 3.95 (2H, t, J=6.5 Hz), 4.47 (2H, q, J=7.2 Hz), 7.82 (1H, s), 8.51 (1H, s).

(2) 4-Butoxy-6,7-dichloro-2-methyl-1-oxo-1,2-dihydro-3-²⁵ isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))

Melting point 209-210°C.

Elemental analysis for $C_{15}H_{15}NO_4Cl_2$

Calculated: C, 52.34; H, 4.39; N, 4.07.

³⁰ Found: C, 52.21; H, 4, 27; N, 3.78.

1H -NMR(CDCl₃) δ: 1.01 (3H, t, J=7.3 Hz), 1.49-1.60 (2H, m), 1.74-1.84 (2H, m), 3.58 (3H, s), 3.99 (2H, t, J=6.6 Hz), 5.03 (1H, bs), 7.83 (1H, s), 8.49 (1H, s).

(3) 4-Butoxy-6,7-dichloro-3-hydroxymethyl-2-methyl-³⁵ 1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))

Melting point 146-147°C.

Elemental analysis for C₁₅H₁₇NO₃Cl₂

Calculated: C, 54.56; H, 5.19; N, 4.24.

Found: C, 54.32; H, 4.98; N, 4.14.

⁵ ¹H-NMR(CDCl₃) δ: 1.04 (3H, t, J=7.3 Hz), 1.44-1.67 (2H, m), 1.77-1.91 (2H, m), 2.52 (1H, bs), 3.71 (3H, s), 3.83 (2H, t, J=6.6 Hz), 4.79 (2H, s), 7.66 (1H, s), 8.38 (1H, s).

(4) 4-Butoxy-3-chloromethyl-6,7-dichloro-2-methyl-1(2H)-

¹⁰ isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

¹H-NMR(CDCl₃) δ: 1.05 (3H, t, J=7.1 Hz), 1.52-1.76 (2H, m), 1.82-1.96 (2H, m), 3.72 (3H, s), 3.97 (2H, t, J=6.5 Hz), 4.77 (2H, s), 7.81 (1H, s), 8.51 (1H, s).

¹⁵ (5) 2-[(4-Butoxy-6,7-dichloro-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl]-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

Melting point 228-228.5°C.

²⁰ Elemental analysis for C₂₃H₂₀N₂O₄Cl₂

Calculated: C, 60.14; H, 4.39; N, 6.10.

Found: C, 59.92; H, 4.35; N, 6.13.

¹H-NMR(CDCl₃) δ: 1.01 (3H, t, J=7.2 Hz), 1.46-1.64 (2H, m), 1.80-1.94 (2H, m), 3.56 (3H, s), 4.03 (2H, t, J=6.8

²⁵ Hz), 5.06 (2H, s), 7.73-7.88 (5H, m), 8.48 (1H, s).

(6) Tert-butyl (4-butoxy-6,7-dichloro-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 1 (6))

³⁰ Melting point 159.5-160°C.

Elemental analysis for C₂₀H₂₆N₂O₄Cl₂

Calculated: C, 55.95; H, 6.10; N, 6.52.

Found: C, 55.93; H, 6.18; N, 6.29.

¹H-NMR(CDCl₃) δ: 1.04 (3H, t, J=7.1 Hz), 1.47 (9H, s),

³⁵ 1.49-1.63 (2H, m), 1.73-1.93 (2H, m), 3.62 (3H, s), 3.83 (2H, t, J=6.6 Hz), 4.52 (2H, d, J=5.4 Hz), 4.82 (1H, bs),

7.75 (1H, s), 8.46 (1H, s).

(7) 3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-methyl-1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1

5 (7))

Melting point 251-252°C.

Elemental analysis for C₁₅H₁₉N₂O₂Cl₂, 1/4H₂O

Calculated: C, 48.67; H, 5.31; N, 7.57.

Found: C, 48.69; H, 5.37; N, 7.79.

10 ¹H-NMR(DMSO-d₆) δ:0.99 (3H, t, J=7:3 Hz), 1.45-1.63 (2H, m), 1.77-1.91 (2H, m), 3.61 (3H, s), 3.92 (2H, t, J=6.4 Hz), 4.23 (2H, s), 7.91 (1H, s), 8.36 (1H, s), 8.79 (3H, bs).

Example 37

15 3-(1-Aminoethyl)-4-butoxy-6,7-dichloro-2-methyl-1(2H)-isoquinolinone hydrochloride

(1) To a solution of dimethyl sulfoxide (1.7 ml, 24 mmol) in tetrahydrofuran (10 mmol) was added oxalyl chloride (1.05 ml, 12 mmol) at -78°C and the obtained

20 mixture was stirred at -78°C for 15 min. To the mixture was added 4-butoxy-6,7-dichloro-3-hydroxymethyl-2-methyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 36 (3)) (2.43 g, 5 mmol) and the obtained mixture was stirred at -78°C for

25 5 min. To the mixture was added triethylamine (5.6 ml, 40 mmol) and the obtained mixture was stirred at room temperature for 30 min. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous

30 magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from tetrahydrofuran - diisopropyl ether to give 4-butoxy-6,7-dichloro-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinealdehyde (2.14 g, 81.7%) as crystals.

35 Melting point 114-115°C.

Elemental analysis for C₁₅H₁₅NO₃Cl₂

Calculated: C, 54.90; H, 4.61; N, 4.27.

Found: C, 54.71; H, 4.39; N, 4.21.

¹H-NMR(CDCl₃) δ: 1.04 (3H, t, J=7.3 Hz), 1.49-1.68 (2H, m), 1.84-1.98 (2H, m), 3.82 (3H, s), 4.05 (2H, t, J=6.6 Hz), 7.96 (2H, s), 8.56 (1H, s), 10.24 (1H, s).

(2) To a solution of 4-butoxy-6,7-dichloro-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinealdehyde (0.98 g, 24 mmol) in tetrahydrofuran (20 mmol) was added 3N methylmagnesium bromide tetrahydrofuran solution(1.5 ml,

10 4.5 mmol) at 0°C and the obtained mixture was stirred at 0°C for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The

15 residue was recrystallized from ethyl acetate - n-hexane to give 4-butoxy-6,7-dichloro-3-(1-hydroxyethyl)-2-methyl-1(2H)-isoquinolinone (0.95 g, 92.2%) as crystals.

Melting point 123-123.5°C.

Elemental analysis for C₁₆H₁₉NO₃Cl₂

20 Calculated: C, 55.83; H, 5.56; N, 4.07..

Found: C, 55.81; H, 5.59; N, 3.86.

¹H-NMR(CDCl₃) δ: 1.04 (3H, t, J=7.3 Hz), 1.49-1.63 (2H, m), 1.64 (3H, d, J=7.0 Hz), 1.78-1.92 (2H, m), 3.26 (1H, bs), 3.70-3.84 (5H, m), 5.63 (1H, q, J=7.0 Hz), 7.59 (1H, s), 8.36 (1H, s).

(3) 4-Butoxy-3-(1-chloroethyl)-6,7-dichloro-2-methyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

¹H-NMR(CDCl₃) δ: 1.05 (3H, t, J=7.3 Hz), 1.51-1.69 (2H, m), 1.82-1.92 (2H, m), 1.96 (3H, d, J=7.2 Hz), 3.83 (3H, s), 3.88-3.96 (2H, m), 5.92-6.00 (1H, m), 7.81 (1H, s), 8.50 (1H, s).

(4) 2-[1-(4-Butoxy-6,7-dichloro-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl)ethyl]-1H-isoindole-1,3(2H)-

35 dione (synthesized according to the method similar to that in Example 4 (6))

Elemental analysis for C₂₄H₂₂N₂O₄Cl₂

Calculated: C, 60.90; H, 4.68; N, 5.92.

Found: C, 60.76; H, 4.38; N, 5.72.

¹H-NMR(C DCl₃) δ: 0.99 (3H, t, J=7.3 Hz), 1.41-1.52 (2H, m), 1.77-1.87 (2H, m), 2.08 (3H, d, J=7.6 Hz), 3.67 (3H, s), 3.84-3.95 (1H, m), 4.05-4.16 (1H, m), 5.81 (1H, q, J=7.6 Hz), 7.72-7.87 (5H, m), 8.47 (1H, s).

(5) Tert-butyl 1-(4-butoxy-6,7-dichloro-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl)ethylcarbamate (synthesized according to the method similar to that in Example 1 (6))

Melting point 118-118.5°C.

Elemental analysis for C₂₁H₂₈N₂O₄Cl₂

Calculated: C, 56.89; H, 6.37; N, 6.32.

¹⁵ Found: C, 57.11; H, 6.58; N, 6.13.

¹H-NMR(CDCl₃) δ: 1.04 (3H, t, J=7.4 Hz), 1.43 (9H, s), 1.54 (3H, d, J=7.0 Hz), 1.56-1.74 (2H, m), 1.84-1.98 (2H, m), 3.73 (3H, s), 3.82-4.03 (2H, m), 5.20-5.29 (1H, m), 5.57 (1H, bs), 7.72 (1H, s), 8.48 (1H, s).

²⁰ (6) 3-(1-Aminoethyl)-4-butoxy-6,7-dichloro-2-methyl-1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 224-225°C.

²⁵ Elemental analysis for C₁₆H₂₁N₂O₂Cl₃

Calculated: C, 50.61; H, 5.57; N, 7.38.

Found: C, 50.38; H, 5.63; N, 7.28.

¹H-NMR(DMSO-d₆) δ: 0.99 (3H, t, J=7.3 Hz), 1.44-1.62 (2H, m), 1.69 (3H, d, J=7.4 Hz), 1.81-1.92 (2H, m), 3.61 (3H, s), 3.92 (2H, t, J=6.8 Hz), 4.95 (2H, bs), 7.87 (1H, s), 8.36 (1H, s), 8.87 (3H, bs).

Example 38

3-(1-Aminobutyl)-4-butoxy-6,7-dichloro-2-methyl-1(2H)-isoquinolinone hydrochloride

³⁵ (1) 4-Butoxy-6,7-dichloro-3-(1-hydroxybutyl)-2-methyl-1(2H)-isoquinolinone (synthesized according to the

- method similar to that in Example 37 (2))
 Melting point 105.5-106°C.
 Elemental analysis for C₁₈H₂₃NO₃Cl₂
 Calculated: C, 58.07; H, 6.23; N, 3.76.
⁵ Found: C, 58.09; H, 6.53; N, 3.57.
¹H-NMR(CDCl₃) δ: 1.00 (3H, t, J=7.3 Hz), 1.04 (3H, t, J=7.3 Hz), 1.31-2.10 (8H, m), 2.98 (1H, bs), 3.75 (3H, s), 3.82 (2H, t, J=6.4 Hz), 5.31-5.40 (1H, m), 7.66 (1H, s), 8.41 (1H, s).
¹⁰ (2) 4-Butoxy-3-(1-chlorobutyl)-6,7-dichloro-2-methyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))
¹H-NMR(CDCl₃) δ: 0.97 (3H, t, J=7.4 Hz), 1.05 (3H, t, J=7.3 Hz), 1.22-1.76 (4H, m), 1.80-1.95 (2H, m), 2.17-
¹⁵ 2.35 (2H, m), 3.79 (3H, s), 3.91 (2H, t, J=6.2 Hz), 5.79 (1H, bs), 7.81 (1H, s), 8.50 (1H, s).
¹(3) 2-[1-(4-Butoxy-6,7-dichloro-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl)butyl]-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to
²⁰ that in Example 4 (6))
 Elemental analysis for C₂₆H₂₆N₂O₄Cl₂
 Calculated: C, 62.28; H, 5.23; N, 5.59.
 Found: C, 62.05; H, 5.02; N, 5.60.
¹H-NMR(CDCl₃) δ: 1.00 (3H, t, J=7.2 Hz), 1.03 (3H, t, J=7.2 Hz), 1.37-1.62 (4H, m), 1.78-1.91 (2H, m), 1.99-
²⁵ 2.17 (1H, m), 2.89-3.08 (1H, m), 3.65 (3H, s), 3.75-3.93 (1H, m), 4.08-4.19 (1H, m), 5.64-5.72 (1H, m), 7.70-7.90 (5H, m), 8.47 (1H, s).
³⁰ (4) Tert-butyl 1-(4-butoxy-6,7-dichloro-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl)butylcarbamate (synthesized according to the method similar to that in Example 1 (6))
 Elemental analysis for C₂₃H₃₂N₂O₄Cl₂
 Calculated: C, 58.60; H, 6.84; N, 5.94.
³⁵ Found: C, 58.67; H, 6.62; N, 5.82.
¹H-NMR(CDCl₃) δ: 0.87 (3H, t, J=7.1 Hz), 1.07 (3H, t,

$J=7.4$ Hz), 1.43 (9H, s), 1.44-1.98 (8H, m), 3.74 (3H, s), 3.82-3.97 (2H, m), 5.12 (1H, bs), 5.37 (1H, bs), 7.71 (1H, s), 8.48 (1H, s).

- (5) 3-(1-Aminobutyl)-4-butoxy-6,7-dichloro-2-methyl-
⁵ 1(2H)-isoquinoline hydrochloride (synthesized according to the method similar to that in Example 1 (7))
 Melting point 217-218°C.

Elemental analysis for $C_{18}H_{25}N_2O_2Cl_3$, 1/2H₂O

Calculated: C, 51.87; H, 6.29; N, 6.72.

¹⁰ Found: C, 51.66; H, 6.44; N, 6.62.

¹H-NMR(DMSO-d₆) δ : 0.92 (3H, t, $J=7.4$ Hz), 0.99 (3H, t, $J=7.4$ Hz), 1.26-1.59 (4H, m), 1.83-2.21 (4H, m), 3.59 (3H, s), 3.82-3.93 (2H, m), 4.88 (1H, bs), 7.88 (1H, s), 8.36 (1H, s), 9.06 (3H, bs).

¹⁵ Example 39

3-(1-Amino-3-methylbutyl)-4-butoxy-6,7-dichloro-2-methyl-1(2H)-isoquinolinone hydrochloride

- (1) 4-Butoxy-6,7-dichloro-3-(1-hydroxy-3-methylbutyl)-2-methyl-1(2H)-isoquinolinone (synthesized according to
²⁰ the method similar to that in Example 37 (2))

Melting point 121-122°C.

Elemental analysis for $C_{19}H_{25}NO_3Cl_2$

Calculated: C, 59.07; H, 6.52; N, 3.63.

Found: C, 59.13; H, 6.54; N, 3.51.

- ²⁵ ¹H-NMR(CDCl₃) δ : 1.02 (6H, d, $J=6.6$ Hz), 1.04 (3H, t, $J=7.4$ Hz), 1.50-1.67 (3H, m), 1.79-2.04 (4H, m), 2.90 (1H, bs), 3.74 (3H, s), 3.77-3.89 (2H, m), 5.39-5.46 (1H, m), 7.66 (1H, s), 8.41 (1H, s).

- (2) 4-Butoxy-3-(1-chloro-3-methylbutyl)-6,7-dichloro-2-methyl-1(2H)-isoquinoline (synthesized according to the
³⁰ method similar to that in Example 4 (5))

¹H-NMR(CDCl₃) δ : 0.95 (3H, d, $J=6.6$ Hz), 0.97 (3H, d, $J=6.6$ Hz), 1.05 (3H, t, $J=7.3$ Hz), 1.52-1.99 (5H, m), 2.13-2.26 (2H, m), 3.79 (3H, s), 3.93 (2H, t, $J=6.6$ Hz),

- ³⁵ 5.90 (1H, bs), 7.81 (1H, s), 8.50 (1H, s).

(3) 2-[1-(4-Butoxy-6,7-dichloro-2-methyl-1-oxo-1,2-

dihydro-3-isoquinolinyl)-3-methylbutyl]-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))
Elemental analysis for C₂₇H₂₈N₂O₄Cl₂

⁵ Calculated: C, 62.69; H, 5.48; N, 5.43.
Found: C, 62.92; H, 5.29; N, 5.39.
¹H-NMR(CDCl₃) δ: 0.81-1.07 (9H, m), 1.40-1.54 (2H, m), 1.63-1.92 (4H, m), 3.03-3.15 (1H, m), 3.72 (3H, s), 3.79-3.90 (1H, m), 4.07-4.19 (1H, m), 5.74-5.82 (1H, m),

¹⁰ 7.72-7.85 (5H, m), 8.47 (1H, s).
(4) Tert-butyl 1-(4-butoxy-6,7-dichloro-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl)-3-methylbutylcarbamate
(synthesized according to the method similar to that in Example 1 (6))

¹⁵ Elemental analysis for C₂₄H₃₄N₂O₄Cl₂

Calculated: C, 59.38; H, 7.06; N, 5.77.

Found: C, 59.31; H, 6.96; N, 5.53.

¹H-NMR(CDCl₃) δ: 0.99 (3H, d, J=6.6 Hz), 1.01 (3H, d, J=6.6 Hz), 1.06 (3H, t, J=7.4 Hz), 1.43 (9H, s), 1.46-

²⁰ 1.69 (4H, m), 1.74-1.95 (3H, m), 3.73 (3H, s), 3.83-3.98 (2H, m), 5.21 (1H, bs), 5.31 (1H, bs), 7.71 (1H, s), 8.48 (1H, s).

(5) 3-(1-Amino-3-methylbutyl)-4-butoxy-6,7-dichloro-2-methyl-1(2H)-isoquinolinone hydrochloride (synthesized

²⁵ according to the method similar to that in Example 1 (7))

Melting point 212.5-213.5°C.

Elemental analysis for C₁₉H₂₇N₂O₂Cl₃

Calculated: C, 54.10; H, 6.45; N, 6.64.

³⁰ Found: C, 53.92; H, 6.55; N, 6.47.

¹H-NMR(DMSO-d₆) δ: 0.93-0.97 (6H, m), 0.99 (3H, t, J=7.4 Hz), 1.42-2.18 (7H, m), 3.59 (3H, s), 3.89 (2H, bs), 5.05 (1H, bs), 7.89 (1H, s), 8.36 (1H, s), 9.18 (3H, bs).

Example 40

³⁵ 3-(1-Aminohexyl)-4-butoxy-6,7-dichloro-2-methyl-1(2H)-isoquinolinone hydrochloride

(1) 4-Butoxy-6,7-dichloro-3-(1-hydroxyhexyl)-2-methyl-1(2H)-isoquinoline (synthesized according to the method similar to that in Example 37 (2))
Melting point 95-96°C.

⁵ Elemental analysis for C₂₀H₂₇NO₃Cl₂

Calculated: C, 60.00; H, 6.80; N, 3.50.

Found: C, 59.90; H, 6.75; N, 3.45.

¹H-NMR(CDCl₃) δ: 0.87-0.93 (3H, m), 1.04 (3H, t, J=7.2 Hz), 1.33-1.35 (4H, m), 1.49-2.05 (8H, m), 2.99 (1H, bs),
¹⁰ 3.74 (3H, s), 3.81 (2H, t, J=6.4 Hz), 5.28-5.38 (1H, m), 7.64 (1H, s), 8.40 (1H, s).

(2) 4-Butoxy-3-(1-chlorohexyl)-6,7-dichloro-2-methyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

¹⁵ ¹H-NMR(CDCl₃) δ: 0.82-0.91 (3H, m), 1.05 (3H, t, J=7.3 Hz), 1.22-1.39 (6H, m), 1.51-1.76 (4H, m), 1.80-1.95 (2H, m), 3.79 (3H, s), 3.91 (2H, t, J=6.2 Hz), 5.78 (1H, bs), 7.81 (1H, s), 8.50 (1H, s).

(3) 2-[1-(4-Butoxy-6,7-dichloro-2-methyl-1-oxo-1,2-dihydro-3-isooquinolinyl)hexyl]-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

Elemental analysis for C₂₈H₃₀N₂O₄Cl₂

Calculated: C, 63.52; H, 5.71; N, 5.29.

²⁵ Found: C, 63.25; H, 5.78; N, 5.03.

¹H-NMR(CDCl₃) δ: 0.90 (3H, t, J=7.0 Hz), 1.00 (3H, t, J=7.3 Hz), 1.30-1.59 (8H, m), 1.77-1.91 (2H, m), 2.01-2.14 (1H, m), 2.97-3.04 (1H, m), 3.70 (3H, s), 3.80-3.92 (1H, m), 4.07-4.18 (1H, m), 5.61-5.69 (1H, m), 7.72-7.85
³⁰ (5H, m), 8.47 (1H, s).

(4) Tert-butyl 1-(4-butoxy-6,7-dichloro-2-methyl-1-oxo-1,2-dihydro-3-isooquinolinyl)hexylcarbamate (synthesized according to the method similar to that in Example 1 (6))

³⁵ Elemental analysis for C₂₅H₃₆N₂O₄Cl₂

Calculated: C, 60.12; H, 7.26; N, 5.61.

Found: C, 59.95; H, 7.04; N, 5.53.

¹H-NMR(CDCl₃) δ: 0.88 (3H, t, J=6.0 Hz), 1.06 (3H, t, J=7.4 Hz), 1.22-1.32 (4H, m), 1.43 (9H, s), 1.50-1.69 (4H, m), 1.74-1.98 (4H, m), 3.73 (3H, s), 3.82-3.96 (2H,

5 m), 5.10-5.12 (1H, m), 5.37 (1H, bs), 7.71 (1H, s), 8.48 (1H, s).

(5) 3-(1-Aminohexyl)-4-butoxy-6,7-dichloro-2-methyl-1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1

10 (7))

Melting point 199.5-200°C.

Elemental analysis for C₂₀H₂₉N₂O₂Cl₃ 1/2H₂O

Calculated: C, 54.00; H, 6.80; N, 6.30.

Found: C, 54.18; H, 6.87; N, 6.14.

15 ¹H-NMR(DMSO-d₆) δ: 0.85-0.88 (3H, m), 0.99 (3H, t, J=7.3 Hz), 1.26-1.62 (7H, m), 1.83-2.18 (4H, m), 3.59 (3H, s), 3.81-3.92 (2H, m), 4.87 (1H, bs), 7.89 (1H, s), 8.36 (1H, s), 9.09 (3H, bs).

Example 41

20 3-[(Aminomethyl)-4-butoxy-6,7-dichloro-1-oxo-2(1H)-isoquinolinyl]-N-isopropylpropanamide hydrochloride
(1) 3-[4-Butoxy-6,7-dichloro-3-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-1-oxo-1,2-dihydro-3-isoquinolinyl]-N-isopropylpropanamide (synthesized

25 according to the method similar to that in Example 35 (8))

Melting point 232-232.5°C.

Elemental analysis for C₂₈H₂₉N₃O₅Cl₂

Calculated: C, 60.22; H, 5.23; N, 7.52.

30 Found: C, 59.98; H, 5.48; N, 7.41.

¹H-NMR(CDCl₃) δ: 0.99 (3H, t, J=7.3 Hz), 1.05 (6H, d, J=6.6 Hz), 1.44-1.59 (2H, m), 1.74-1.91 (2H, m), 2.66 (2H, t, J=6.8 Hz), 3.92 (2H, t, J=6.8 Hz), 3.92-4.02 (1H, m), 4.47 (2H, t, J=7.0 Hz), 5.15 (2H, s), 5.76 (2H, d, J=7.6 Hz), 7.70-7.86 (5H, m), 8.43 (1H, s).

35 (2) Tert-butyl {4-butoxy-6,7-dichloro-2-{3-

(isopropylamino)-3-oxopropyl}-1-oxo-1,2-dihydro-3-isoquinolinyl}methylcarbamate (synthesized according to the method similar to that in Example 1 (6))
Melting point 221-221.5°C.

⁵ Elemental analysis for C₂₅H₃₅N₃O₅Cl₂

Calculated: C, 56.82; H, 6.68; N, 7.95.

Found: C, 56.72; H, 6.51; N, 7.93.

¹H-NMR(CDCl₃) δ: 1.03 (3H, t, J=7.1 Hz), 1.06 (6H, d, J=6.6 Hz), 1.46 (9H, s), 1.51-1.66 (2H, m), 1.74-1.94

¹⁰ (2H, m), 2.71 (2H, t, J=7.0 Hz), 3.87 (3H, t, J=6.6 Hz), 3.94-4.08 (1H, m), 4.35 (2H, t, J=7.0 Hz), 4.56 (2H, d, J=5.8 Hz), 5.69 (1H, bs), 6.01 (1H, bs), 7.79 (1H, s), 8.43 (1H, s).

¹⁵ (3) 3-[(Aminomethyl)-4-butoxy-6,7-dichloro-1-oxo-2(1H)-isoquinolinyl]-N-isopropylpropanamide hydrochloride (synthesized according to the method similar to that in Example 1 (7)).

Melting point 189-191°C.

Elemental analysis for C₂₀H₂₈N₃O₃Cl₃ 2H₂O

²⁰ Calculated: C, 47.96; H, 6.44; N, 8.39.

Found: C, 48.07; H, 6.05; N, 8.36.

¹H-NMR(DMSO-d₆) δ: 0.95 (6H, d, J=6.6 Hz), 0.99 (3H, t, J=7.3 Hz), 1.44-1.63 (2H, m), 1.77-1.91 (2H, m), 2.56 (2H, t, J=6.6 Hz), 3.71-3.82 (1H, m), 3.91 (2H, t, J=6.6 Hz), 4.20-4.31 (4H, m), 4.84 (2H, s), 7.92 (1H, s), 8.02 (1H, d, J=7.4 Hz), 8.38 (1H, s), 8.75 (3H, bs).

Example 42

3-[(Aminomethyl)-4-butoxy-6,7-dichloro-1-oxo-2(1H)-isoquinolinyl]-N-phenylpropanamide hydrochloride

³⁰ (1) 3-[4-Butoxy-6,7-dichloro-3-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-1-oxo-1,2-dihydro-3-isoquinolinyl]-N-phenylpropanamide (synthesized according to the method similar to that in Example 35 (8)).

³⁵ Melting point 204-206°C.

Elemental analysis for C₃₁H₂₇N₃O₅Cl₂

Calculated: C, 62.84; H, 4.59; N, 7.09.

Found: C, 62.46; H, 4.66; N, 7.08.

¹H-NMR(CDCl₃) δ:0.97 (3H, t, J=7.3 Hz), 1.38-1.57 (2H, m), 1.78-1.89 (2H, m), 2.88 (2H, t, J=6.8 Hz), 3.87 (2H, t, J=6.8 Hz), 4.57 (2H, t, J=6.6 Hz), 5.16 (2H, s), 7.03-7.10 (1H, m), 7.23-7.31 (2H, m), 7.46-7.51 (2H, m), 7.69-7.85 (5H, m), 8.34 (1H, s), 8.52 (1H, s).

(2) Tert-butyl {2-(2-anilino-3-oxopropyl)-4-butoxy-6,7-dichloro-1-oxo-1,2-dihydro-3-

¹⁰ isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 1. (6))
Melting point 219-220°C.

Elemental analysis for C₂₈H₃₃N₃O₅Cl₂

Calculated: C, 59.79; H, 5.91; N, 7.47.

¹⁵ Found: C, 59.92; H, 5.84; N, 7.42.
¹H-NMR(CDCl₃) δ:1.03 (3H, t, J=7.3 Hz), 1.46 (9H, s), 1.47-1.65 (2H, m), 1.78-1.93 (2H, m), 2.90 (2H, t, J=7.2 Hz), 3.83 (2H, t, J=6.6 Hz), 4.48 (2H, t, J=7.2 Hz), 4.60 (2H, d, J=5.8 Hz), 5.34 (1H, bs), 7.04-7.11 (1H, m), 7.25-7.33 (2H, m), 7.55-7.59 (2H, m), 7.76 (1H, s), 8.41 (1H, s), 8.72 (1H, bs).

(3) 3-{3-(Aminomethyl)-4-butoxy-6,7-dichloro-1-oxo-2(1H)-isoquinolinyl}-N-phenylpropanamide hydrochloride (synthesized according to the method similar to that in

²⁵ Example 1 (7))

Melting point 243-244°C.

Elemental analysis for C₂₃H₂₆N₃O₃Cl₃

Calculated: C, 55.38; H, 5.25; N, 8.42.

Found: C, 55.31; H, 5.45; N, 8.27.

³⁰ ¹H-NMR(DMSO-d₆) δ:0.97 (3H, t, J=7.3 Hz), 1.40-1.60 (2H, m), 1.73-1.87 (2H, m), 2.83 (2H, t, J=6.4 Hz), 3.84 (2H, t, J=6.4 Hz), 4.31-4.34 (4H, m), 6.99-7.06 (1H, m), 7.23-7.31 (2H, m), 7.54-7.58 (2H, m), 7.91 (1H, s), 8.40 (1H, s), 8.65 (3H, bs), 10.23 (1H, s).

³⁵ Example 43

3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-{3-oxo-3-(1,3-

thiazolidin-3-yl)propyl}-1(2H)-isoquinolinone
hydrochloride

(1) 2-[4-Butoxy-6,7-dichloro-1-oxo-2-{3-oxo-3-(1,3-thiazolidin-3-yl)propyl}methyl]-1H-isoindole-1,3(2H)-
5 dione (synthesized according to the method similar to
that in Example 35 (8))

Melting point 218-220°C.

Elemental analysis for C₂₈H₂₇N₃O₅Cl₂S 1/4H₂O

Calculated: C, 56.71; H, 4.67; N, 7.09.

10 Found: C, 56.66; H, 4.58; N, 6.92.

¹H-NMR(CDCl₃) δ: 0.99 (3H, t, J=7.2 Hz), 1.42-1.60 (2H,
m), 1.77-1.91 (2H, m), 2.80-2.94 (2H, m), 2.98 (2H, t,
J=6.3 Hz), 3.60 (1H, t, J=6.2 Hz), 3.72 (1H, t, J=6.2
Hz), 3.95 (2H, t, J=6.3 Hz), 4.35-4.47 (4H, m), 5.21 (2H,
15 s), 7.71-7.86 (5H, m), 8.46 (1H, s).

(2) Tert-butyl {4-butoxy-6,7-dichloro-1-oxo-2-{3-oxo-3-(1,3-thiazolidin-3-yl)propyl}-1,2-dihydro-3-
isoquinolinyl)methylcarbamate (synthesized according to
the method similar to that in Example 1 (6))

20 Melting point 218-218.5°C.

Elemental analysis for C₂₅H₃₃N₃O₅Cl₂S

Calculated: C, 53.71; H, 5.96; N, 7.52.

Found: C, 54.08; H, 6.20; N, 7.35.

¹H-NMR(CDCl₃) δ: 1.03 (3H, t, J=7.3 Hz), 1.45 (9H, s),
25 1.51-1.63 (2H, m), 1.80-1.94 (2H, m), 2.89-3.00 (2H, m),
3.06 (2H, t, J=6.2 Hz), 3.69-3.91 (4H, m), 4.38 (2H, t,
J=6.8 Hz), 4.46 (1H, s), 4.54 (1H, s), 4.61 (2H, d,
J=5.6 Hz), 5.40 (1H, bs), 7.79 (1H, s), 8.45 (1H, s).
(3) 3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-{3-oxo-3-

30 (1,3-thiazolidin-3-yl)propyl}-1(2H)-isoquinolinone
hydrochloride (synthesized according to the method
similar to that in Example 1 (7))

Melting point 206-207°C.

Elemental analysis for C₂₀H₂₆N₃O₃Cl₃S

35 Calculated: C, 48.54; H, 5.30; N, 8.49.

Found: C, 48.19; H, 5.19; N, 8.36.

¹H-NMR(DMSO-d₆) δ: 0.99 (3H, t, J=7.3 Hz), 1.45-1.64 (2H, m), 1.78-1.92 (2H, m), 2.84 (2H, bs), 2.97 (1H, t, J=6.2 Hz), 3.06 (1H, t, J=6.2 Hz), 3.46 (2H, s), 3.65 (2H, q, J=6.2 Hz), 3.93 (2H, t, J=6.4 Hz), 4.27 (2H, d, J=6.6 Hz), 4.44 (1H, s), 4.50 (1H, s), 7.92 (1H, s), 8.38 (1H, s), 8.66 (3H, bs).

Example 44

(2S)-1-[3-[3-(Aminomethyl)-4-butoxy-6,7-dichloro-1-oxo-2(1H)-isoquinolinyl]propanoyl]-2-pyrrolidinecarboxamide

10 hydrochloride

(1) (2S)-1-[3-[4-Butoxy-6,7-dichloro-3-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-1-oxo-2(1H)-isoquinolinyl]propanoyl]-2-pyrrolidinecarboxamide

(synthesized according to the method similar to that in

15 Example 35 (8))

Melting point 235-236.5°C.

Elemental analysis for C₃₀H₃₀N₄O₆Cl₂ 1/2H₂O

Calculated: C, 57.88; H, 5.02; N, 9.00.

Found: C, 57.86; H, 4.94; N, 8.90.

20 ¹H-NMR(CDCl₃) δ: 1.00 (3H, t, J=7.3 Hz), 1.43-1.62 (2H, m), 1.69-1.99 (4H, m), 2.33-2.42 (1H, m), 2.67-2.89 (2H, m), 3.22-3.29 (2H, m), 3.98 (2H, t, J=6.6 Hz), 4.35-4.49 (2H, m), 5.16 (2H, d, J=2.2 Hz), 5.37 (1H, bs), 7.06 (1H, bs), 7.72-7.86 (5H, m), 8.44 (1H, s).

25 (2) Tert-butyl (2-{3-[(2S)-2-(aminocarbonyl)pyrrolizinyl]-3-oxopropyl}-4-butoxy-6,7-dichloro-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 1 (6))

30 Melting point 159-160°C.

Elemental analysis for C₂₆H₃₅N₃O₅Cl₂

Calculated: C, 57.78; H, 6.53; N, 7.77.

Found: C, 57.95; H, 6.43; N, 7.60.

¹H-NMR(CDCl₃) δ: 1.03 (3H, t, J=7.2 Hz), 1.43 (9H, s),

35 1.53-1.73 (4H, m), 1.83-2.00 (4H, m), 2.33-2.42 (1H, m), 2.79-2.98 (2H, m), 3.37-3.65 (2H, m), 3.87 (2H, t, J=6.5

Hz), 4.24-4.44 (2H, m), 4.55 (2H, d, J=6.4 Hz), 5.34 (1H, bs), 5.41 (1H, bs), 7.13 (1H, bs), 7.79 (1H, s), 8.42 (1H, s).

(3) (2S)-1-[3-[3-(Aminomethyl)-4-butoxy-6,7-dichloro-1-oxo-2(1H)-isoquinolinyl]propanoyl]-2-pyrrolidinecarboxamide hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 185-185.5°C.

10 Elemental analysis for $C_{22}H_{29}N_4O_4Cl_3 \cdot 1/2H_2O$

Calculated: C, 49.96; H, 5.72; N, 10.59.

Found: C, 50.12; H, 5.79; N, 10.29.

1H -NMR(DMSO-d₆) δ : 1.00 (3H, t, J=7.3 Hz), 1.45-1.64 (2H, m), 1.72-1.99 (5H, m), 2.65-2.83 (2H, m), 3.33-3.55 (4H, m), 3.93 (2H, t, J=6.4 Hz), 4.08-4.28 (4H, m), 6.94 (1H, bs), 7.35 (1H, bs), 7.92 (1H, s), 8.38 (1H, s), 8.72 (3H, bs).

Example 45

(2S)-1-[3-[3-(Aminomethyl)-4-butoxy-6,7-dichloro-1-oxo-2(1H)-isoquinolinyl]propanoyl]-2-pyrrolidine carbonitrile hydrochloride

(1) A solution of tert-butyl (2-{3-[{(2S)-2-(aminocarbonyl)pyrrolizinyl]-3-oxopropyl}-4-butoxy-6,7-dichloro-1-oxo-1,2-dihydro-3-isooquinolinyl}-methylcarbamate (Example 44 (1)) (0.58 g, 1 mmol) and cyanuric chloride (0.54 g, 3 mmol) in N,N-dimethylformamide (50 mmol) was stirred at 0°C for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from tetrahydrofuran - diisopropyl ether to give tert-butyl (4-butoxy-6,7-dichloro-2-{3-[{(2S)-2-cyanopyrrolizinyl]-3-oxopropyl}-1-oxo-1,2-dihydro-3-isooquinolinyl)methylcarbamate (0.39 g, 69.6%) as crystals.

Melting point 181-183°C.

Elemental analysis for C₂₇H₃₄N₄O₅Cl₂

Calculated: C, 57.35; H, 6.06; N, 9.91.

Found: C, 57.16; H, 6.24; N, 9.61.

5 ¹H-NMR(CDCl₃) δ:1.03 (3H, t, J=7.4 Hz), 1.45 (9H, s),
1.51-1.63 (2H, m), 1.76-1.94 (2H, m), 2.11-2.32 (4H, m),
2.91 (2H, t, J=6.8 Hz), 3.44-3.51 (1H, m), 3.62-3.67 (1H,
m), 3.88 (2H, t, J=6.6 Hz), 4.40 (2H, t, J=6.8 Hz), 4.61
(2H, d, J=5.6 Hz), 4.63-4.72 (1H, m), 5.38 (1H, s), 7.79
(1H, s), 8.44 (1H, s).

(2) (2S)-1-[3-[3-(Aminomethyl)-4-butoxy-6,7-dichloro-1-oxo-2(1H)-isoquinolinyl]propanoyl]-2-pyrrolidine carbonitrile hydrochloride (synthesized according to the method similar to that in Example 1 (7))

15 ¹H-NMR(DMSO-d₆) δ:0.99 (3H, t, J=7.3 Hz), 1.47-1.64 (2H,
m), 1.71-2.19 (6H, m), 2.78-2.88 (2H, m), 3.36-3.82 (2H,
m), 3.93 (2H, t, J=6.4 Hz), 4.16-4.58 (5H, m), 7.93 (1H,
s), 8.38 (1H, s), 8.64 (3H, bs).

Example 46

20 3-(Aminomethyl)-4-butoxy-2-neopentyl-1(2H)-isoquinolinone hydrochloride

(1) Ethyl 4-hydroxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (1))

25 Melting point 72-72.5°C.

Elemental analysis for C₁₇H₂₁NO₄ 1/4H₂O

Calculated: C, 66.32; H, 7.04; N, 4.55.

Found: C, 66.40; H, 7.14; N, 4.54.

¹H-NMR(CDCl₃) δ:0.85 (9H, s), 1.47 (3H, t, J=7.2 Hz),

30 4.48 (2H, q, J=7.2 Hz), 4.54 (2H, bs), 7.69-7.80 (2H, m),
8.13-8.18 (1H, m), 8.44-8.49 (1H, m), 10.85 (1H, s).

(2) Ethyl 4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (2))

35 ¹H-NMR(CDCl₃) δ:0.94 (9H, s), 1.01 (3H, t, J=7.3 Hz),
1.44 (3H, t, J=7.2 Hz), 1.44-1.60 (2H, m), 1.74-1.84 (2H,

m), 3.96 (2H, t, J=6.6 Hz), 4.11 (2H, bs), 4.43 (2H, q, J=7.2 Hz), 7.51-7.61 (1H, m), 7.68-7.81 (2H, m), 8.43-8.47 (1H, m).

(3) 4-Butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-

- ⁵ isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))
Melting point 146-148°C.

¹H-NMR(CDCl₃) δ: 0.96 (9H, s), 1.00 (3H, t, J=7.4 Hz), 1.46-1.65 (2H, m), 1.76-1.90 (2H, m), 4.01 (2H, t, J=6.6 Hz), 4.19 (2H, bs), 5.71 (1H, bs), 7.51-7.60 (1H, m), 7.67-7.86 (2H, m), 8.41-8.45 (1H, m).

(4) 4-Butoxy-3-hydroxymethyl-2-neopentyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))

¹⁵ Melting point 123-124°C.

Elemental analysis for C₁₉H₂₇NO₃

Calculated: C, 70.89; H, 8.61; N, 4.35.

Found: C, 71.29; H, 8.23; N, 4.36.

¹H-NMR(CDCl₃) δ: 1.00 (9H, s), 1.07 (3H, t, J=7.3 Hz), 1.50-1.68 (2H, m), 1.80-1.94 (2H, m), 2.35 (1H, bs), 3.91 (2H, t, J=6.4 Hz), 4.22 (2H, bs), 4.89 (2H, bs), 7.42-7.50 (1H, m), 7.60-7.72 (2H, m), 8.35 (1H, d, J=8.1 Hz).

(5) 4-Butoxy-3-chloromethyl-2-neopentyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

¹H-NMR(CDCl₃) δ: 0.99 (9H, s), 1.04 (3H, t, J=7.1 Hz), 1.52-1.69 (2H, m), 1.82-1.96 (2H, m), 3.96 (2H, t, J=6.6 Hz), 4.18 (2H, bs), 4.90 (2H, bs), 7.50-7.58 (1H, m), 7.66-7.78 (2H, m), 8.42-8.46 (1H, m).

(6) 2-[(4-Butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl]-1H-isoindole-1,3(2H)-dione
(synthesized according to the method similar to that in Example 4 (6))

³⁵ Melting point 132.5-133°C.

Elemental analysis for C₂₇H₃₀N₂O₄ 1/4H₂O

Calculated: C, 71.90; H, 6.82; N, 6.21.

Found: C, 72.18; H, 6.73; N, 6.12.

¹H-NMR(CDCl₃) δ:1.00 (3H, t, J=7.3 Hz), 1.01 (9H, s), 1.45-1.60 (2H, m), 1.82-1.96 (2H, m), 4.03 (2H, t, J=6.8 Hz), 4.14 (2H, bs), 5.09 (2H, s), 7.46-7.54 (1H, m), 7.64-7.83 (6H, m), 8.39-8.43 (1H, m).

(7) Tert-butyl (4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 1 (6))

10 Melting point 138-139°C.

Elemental analysis for C₂₄H₃₆N₂O₄

Calculated: C, 69.20; H, 8.71; N, 6.73.

Found: C, 69.30; H, 8.80; N, 6.70.

¹H-NMR(CDCl₃) δ:1.00 (9H, s), 1.03 (3H, t, J=7.4 Hz), 1.45 (9H, s), 1.53-1.65 (2H, m), 1.76-1.94 (2H, m), 3.87 (2H, t, J=6.6 Hz), 4.14 (2H, bs), 4.58 (2H, d, J=5.2 Hz), 4.66 (1H, bs), 7.46-7.54 (1H, m), 7.64-7.73 (2H, m), 8.40-8.44 (1H, m).

(8) 3-(Aminomethyl)-4-butoxy-2-neopentyl-1(2H)-

20 isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 231-232°C.

Elemental analysis for C₁₉H₂₉N₂O₂Cl

Calculated: C, 64.67; H, 8.28; N, 7.94.

25 Found: C, 64.61; H, 8.44; N, 7.76.

¹H-NMR(DMSO-d₆) δ:0.91 (9H, s), 0.99 (3H, t, J=7.3 Hz), 1.48-1.62 (2H, m), 1.78-1.92 (2H, m), 3.94 (2H, t, J=6.4 Hz), 4.11 (2H, bs), 4.25 (2H, bs), 7.58-7.67 (1H, m), 7.77-7.90 (2H, m), 8.27-8.30 (1H, m), 8.59 (3H, bs).

30 Example 47

3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-(2-furylmethyl)-1(2H)-isoquinolinone hydrochloride

(1) Ethyl 6,7-dichloro-2-(2-furylmethyl)-4-hydroxy-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized

35 according to the method similar to that in Example 1 (1))

Melting point 134-135°C.

Elemental analysis for $C_{17}H_{13}NO_5Cl_2$

Calculated: C, 53.42; H, 3.43; N, 3.66.

Found: C, 53.84; H, 3.53; N, 3.44.

⁵ 1H -NMR(CDCl₃) δ: 1.42 (3H, t, J=7.2 Hz), 4.42 (2H, q, J=7.2 Hz), 5.68 (2H, s), 6.16 (1H, dd, J=0.8, 3.1 Hz), 6.27 (1H, dd, J=2.0, 3.1 Hz), 7.28 (1H, dd, J=0.8, 2.0 Hz), 8.21 (1H, s), 8.54 (1H, s), 11.11 (1H, s).

(2) Ethyl 4-butoxy-6,7-dichloro-2-(2-furylmethyl)-1-oxo-

¹⁰ 1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (2))

1H -NMR(CDCl₃) δ: 1.00 (3H, t, J=7.4 Hz), 1.37 (3H, t, J=7.1 Hz), 1.42-1.61 (2H, m), 1.71-1.85 (2H, m), 3.92

¹⁵ (2H, t, J=6.4 Hz), 4.39 (2H, q, J=7.1 Hz), 5.36 (2H, s), 6.28-6.32 (2H, m), 7.32 (1H, d, J=1.5 Hz), 7.81 (1H, s), 8.53 (1H, s).

(3) 4-Butoxy-6,7-dichloro-2-(2-furylmethyl)-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized

²⁰ according to the method similar to that in Example 4 (3))

Melting point 147.5-148°C.

Elemental analysis for $C_{19}H_{17}NO_5Cl_2$

Calculated: C, 57.59; H, 4.83; N, 3.53.

²⁵ Found: C, 57.40; H, 4.79; N, 3.37.

1H -NMR(CDCl₃) δ: 0.99 (3H, t, J=7.3 Hz), 1.47-1.62 (2H, m), 1.75-1.89 (2H, m), 4.00 (2H, t, J=6.6 Hz), 5.16 (1H, bs), 5.52 (2H, s), 6.28 (1H, dd, J=1.8, 3.2 Hz), 6.35 (1H, dd, J=0.8, 3.2 Hz), 7.30 (1H, dd, J=0.8, 1.8 Hz),

³⁰ 7.82 (1H, s), 8.54 (1H, s).

(4) 4-Butoxy-6,7-dichloro-2-(2-furylmethyl)-3-hydroxymethyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))

³⁵ Melting point 120-121°C.

Elemental analysis for $C_{19}H_{19}NO_5Cl_2$

Calculated: C, 57.59; H, 4.83; N, 3.53.

Found: C, 57.40; H, 4.79; N, 3.37.

¹H-NMR(CDCl₃) δ: 1.04 (3H, t, J=7.3 Hz), 1.49-1.62 (2H, m), 1.78-1.92 (2H, m), 3.88 (2H, t, J=6.5 Hz), 4.97 (2H, d, J=5.4 Hz), 5.49 (2H, s), 6.32 (1H, dd, J=1.8, 2.9 Hz), 6.40 (1H, dd, J=0.8, 2.9 Hz), 7.31 (1H, dd, J=0.8, 1.8 Hz), 7.75 (1H, s), 8.45 (1H, s).

(5) 4-Butoxy-3-chloromethyl-6,7-dichloro-2-(2-furylmethyl)-1(2H)-isoquinoline (synthesized according

¹⁰ to the method similar to that in Example 4 (5))

¹H-NMR(CDCl₃) δ: 1.05 (3H, t, J=7.3 Hz), 1.55-1.79 (2H, m), 1.82-1.93 (2H, m), 3.99 (2H, t, J=6.6 Hz), 5.00 (2H, s), 5.46 (2H, s), 6.31 (1H, dd, J=1.9, 3.2 Hz), 6.41 (1H, dd, J=1.1, 3.2 Hz), 7.31 (1H, dd, J=1.1, 1.9 Hz), 7.81

¹⁵ (1H, s), 8.51 (1H, s).

(6) 2-{(4-Butoxy-6,7-dichloro-2-(2-furylmethyl)-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl}-1H-isoindole-1,3(2H)-dione. (synthesized according to the method similar to that in Example 4 (6))

²⁰ Melting point 148-149°C.

Elemental analysis for C₂₇H₂₂N₂O₅Cl₂

Calculated: C, 61.72; H, 4.22; N, 5.33.

Found: C, 61.95; H, 4.51; N, 5.47...

¹H-NMR(CDCl₃) δ: 1.01 (3H, t, J=7.3 Hz), 1.45-1.63 (2H,

²⁵ m), 1.80-1.94 (2H, m), 4.02 (2H, t, J=6.8 Hz), 5.15 (2H, s), 5.36 (2H, s), 6.05 (1H, dd, J=1.8, 3.2 Hz), 6.17 (1H, dd, J=0.8, 3.2 Hz), 6.89 (1H, dd, J=0.8, 1.8 Hz), 7.69-7.80 (4H, bs), 7.82 (1H, s), 8.49 (1H, s).

(7) Tert-butyl (4-butoxy-6,7-dichloro-2-(2-furylmethyl)-

³⁰ 1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 1 (6))

Melting point 143-144°C.

Elemental analysis for C₂₄H₂₈N₂O₅Cl₂

³⁵ Calculated: C, 58.19; H, 5.70; N, 5.65.

Found: C, 58.31; H, 5.53; N, 5.70.

- ¹H-NMR(CDCl₃) δ: 1.04 (3H, t, J=7.3 Hz), 1.46 (9H, s), 1.51-1.67 (2H, m), 1.79-1.93 (2H, m), 3.84 (2H, t, J=6.5 Hz), 4.66 (2H, d, J=5.8 Hz), 4.91 (1H, bs), 5.37 (2H, s), 6.30 (1H, dd, J=2.0, 3.4 Hz), 6.44 (1H, d, J=3.4 Hz),
⁵ 7.32 (1H, d, J=2.0 Hz), 7.75 (1H, s), 8.47 (1H, s).
- (8) 3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-(2-furylmethyl)-1(2H)-isoquinolinone hydrochloride
 (synthesized according to the method similar to that in Example 1 (7))
- ¹⁰ Melting point 223-224°C.
- Elemental analysis for C₁₉H₂₁N₂O₃Cl₃
 Calculated: C, 52.86; H, 4.90; N, 6.49.
 Found: C, 52.55; H, 4.97; N, 6.58.
- ¹H-NMR(DMSO-d₆) δ: 0.99 (3H, t, J=7.3 Hz), 1.44-1.63 (2H, m), 1.77-1.92 (2H, m), 3.94 (2H, t, J=6.4 Hz), 4.26 (2H, s), 5.40 (2H, s), 6.42 (1H, dd, J=1.8, 3.2 Hz), 6.45 (1H, dd, J=1.0, 3.2 Hz), 7.61 (1H, dd, J=1.0, 1.8 Hz), 7.93 (1H, s), 8.39 (1H, s), 8.82 (3H, bs)..
- Example 48**
- ²⁰ 3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-(2-methoxyethyl)-1(2H)-isoquinolinone hydrochloride
 (1) Ethyl 6,7-dichloro-4-hydroxy-2-(2-methoxyethyl)-1-oxo-1,2-dihydro-3-isouinolinecarboxylate (synthesized according to the method similar to that in Example 1
²⁵ (1))
 Melting point 110.5-111°C.
- Elemental analysis for C₁₅H₁₅NO₅Cl₂
 Calculated: C, 50.02; H, 4.20; N, 3.89.
 Found: C, 49.86; H, 4.44; N, 3.76.
- ³⁰ ¹H-NMR(CDCl₃) δ: 1.46 (3H, t, J=7.1 Hz), 3.30 (3H, s), 3.62 (2H, d, J=5.8 Hz), 4.49 (2H, q, J=7.1 Hz), 4.61 (2H, t, J=5.8 Hz), 8.22 (1H, s), 8.51 (1H, s), 10.95 (1H, s).
 (2) Ethyl 4-butoxy-6,7-dichloro-2-(2-methoxyethyl)-1-oxo-1,2-dihydro-3-isouinolinecarboxylate (synthesized
³⁵ according to the method similar to that in Example 1 (2))

Melting point 102-103°C.

Elemental analysis for C₁₉H₂₃NO₅Cl₂

Calculated: C, 54.82; H, 5.57; N, 3.36.

Found: C, 54.81; H, 5.35; N, 3.36.

5 ¹H-NMR(CDCl₃) δ: 1.01 (3H, t, J=7.3 Hz), 1.44 (3H, t, J=7.2 Hz), 1.50-1.62 (2H, m), 1.72-1.86 (2H, m), 3.31 (3H, s), 3.63 (2H, t, J=5.9 Hz), 3.94 (2H, t, J=6.4 Hz), 4.26 (2H, t, J=5.9 Hz), 4.45 (2H, q, J=7.2 Hz), 7.82 (1H, s), 8.50 (1H, s).

10 (3) 4-Butoxy-6,7-dichloro-2-(2-methoxyethyl)-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))

Melting point 142-143°C.

15 Elemental analysis for C₁₇H₁₉NO₅Cl₂

Calculated: C, 52.59; H, 4.93; N, 3.61.

Found: C, 52.58; H, 4.94; N, 3.41.

¹H-NMR(CDCl₃) δ: 1.00 (3H, t, J=7.2 Hz), 1.44-1.63 (2H, m), 1.74-1.89 (2H, m), 3.41 (3H, s), 3.85 (2H, t, J=5.3 Hz), 4.00 (2H, t, J=6.4 Hz), 4.37-4.40 (2H, m), 7.82 (1H, s), 8.48 (1H, s).

 (4) 4-Butoxy-6,7-dichloro-3-hydroxymethyl-2-(2-methoxyethyl)-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4

25 (4))

Melting point 122-123°C.

Elemental analysis for C₁₇H₂₁NO₄Cl₂

Calculated: C, 54.56; H, 5.66; N, 3.74.

Found: C, 54.34; H, 5.59; N, 3.57.

30 ¹H-NMR(CDCl₃) δ: 1.04 (3H, t, J=7.3 Hz), 1.50-1.69 (2H, m), 1.80-1.94 (2H, m), 3.34 (3H, s), 3.83 (2H, t, J=5.5 Hz), 3.96 (2H, t, J=6.6 Hz), 4.38 (2H, t, J=5.5 Hz), 4.46 (1H, t, J=6.4 Hz), 4.79 (2H, d, J=6.4 Hz), 7.84 (1H, s), 8.47 (1H, s).

35 (5) 4-Butoxy-3-chloromethyl-6,7-dichloro-2-(2-methoxyethyl)-1(2H)-isoquinolinone (synthesized

according to the method similar to that in Example 4

(5))

$^1\text{H-NMR}(\text{CDCl}_3)$ δ : 1.05 (3H, t, $J=7.3$ Hz), 1.55-1.70 (2H, m), 1.82-1.96 (2H, m), 3.26 (3H, s), 3.69 (2H, t, $J=4.8$

5 Hz), 3.98 (2H, t, $J=6.4$ Hz), 4.43 (2H, t, $J=4.8$ Hz), 4.99 (2H, s), 7.82 (1H, s), 8.50 (1H, s).

(6) 2-{{(4-Butoxy-6,7-dichloro-2-(2-methoxyethyl)-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl}-1H-isoinole-1,3(2H)-dione (synthesized according to the method

10 similar to that in Example 4 (6))

Melting point 151-152°C.

Elemental analysis for $\text{C}_{25}\text{H}_{24}\text{N}_2\text{O}_5\text{Cl}_2$

Calculated: C, 59.65; H, 4.81; N, 5.57.

Found: C, 59.52; H, 4.85; N, 5.55.

15 $^1\text{H-NMR}(\text{CDCl}_3)$ δ : 1.00 (3H, t, $J=7.3$ Hz), 1.44-1.62 (2H, m), 1.79-1.93 (2H, m), 2.97 (3H, s), 3.64 (2H, t, $J=4.9$ Hz), 3.98 (2H, t, $J=6.6$ Hz), 4.37 (2H, t, $J=4.9$ Hz), 5.10 (2H, s); 7.68-7.87 (5H, m), 8.47 (1H, s).

(7) Tert-butyl {4-butoxy-6,7-dichloro-2-(2-

20 methoxyethyl)-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 1 (6))

Melting point 137-138°C.

Elemental analysis for $\text{C}_{22}\text{H}_{30}\text{N}_2\text{O}_5\text{Cl}_2$

25 Calculated: C, 55.82; H, 6.39; N, 5.92.

Found: C, 55.99; H, 6.33; N, 5.76.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ : 1.03 (3H, t, $J=7.3$ Hz), 1.46 (9H, s), 1.51-1.64 (2H, m), 1.81-1.95 (2H, m), 3.33 (3H, s), 3.80 (2H, t, $J=4.5$ Hz), 3.85 (2H, t, $J=6.6$ Hz), 4.30 (2H, t, $J=4.5$ Hz), 4.54 (2H, d, $J=5.2$ Hz), 6.15 (1H, bs), 7.80 (1H, s), 8.46 (1H, s).

(8) 3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-(2-methoxyethyl)-1(2H)-isoquinolinone hydrochloride

(synthesized according to the method similar to that in

35 Example 1 (7))

Melting point 241.5-242°C.

Elemental analysis for C₁₇H₂₃N₂O₃Cl₃

Calculated: C, 49.83; H, 5.66; N, 6.84.

Found: C, 49.80; H, 5.91; N, 6.81.

¹H-NMR(DMSO-d₆) δ: 0.99 (3H, t, J=7.3 Hz), 1.45-1.63 (2H, m), 1.77-1.91 (2H, m), 3.24 (3H, s), 3.61 (2H, d, J=4.9 Hz), 3.93 (2H, t, J=6.6 Hz), 4.23-4.32 (4H, m), 7.91 (1H, s), 8.38 (1H, s), 8.68 (3H, bs).

Example 49

3-(Aminomethyl)-4-(2-methoxyethoxy)-2-neopentyl-1(2H)-
10 isoquinolinone hydrochloride

(1) Ethyl 4-(2-methoxyethoxy)-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (2))

¹H-NMR(CDCl₃) δ: 0.94 (9H, s), 1.43 (3H, t, J=7.2 Hz), 3.48 (3H, s), 3.71-3.75 (2H, m), 4.07-4.17 (2H, m), 4.43 (2H, q, J=7.2 Hz), 7.53-7.61 (1H, m), 7.69-7.77 (1H, m), 7.93-7.97 (1H, m), 8.42-8.47 (1H, m).

(2) 4-(2-Methoxyethoxy)-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to
20 the method similar to that in Example 4 (3))

Melting point 148-149°C.

Elemental analysis for C₁₈H₂₃NO₅

Calculated: C, 64.85; H, 6.95; N, 4.20.

Found: C, 64.79; H, 6.96; N, 4.09.

25 ¹H-NMR(CDCl₃) δ: 0.94 (9H, s), 3.49 (3H, s), 3.76-3.81 (2H, m), 4.27-4.32 (4H, m), 7.56-7.64 (1H, m), 7.70-7.78 (1H, m), 7.89 (1H, dd, J=0.8, 8.0 Hz), 8.44 (1H, dd, J=1.0, 8.0 Hz), 9.79 (1H, bs).

(3) 3-Hydroxymethyl-4-(2-methoxyethoxy)-2-neopentyl-
30 1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))

Melting point 145-145.5°C.

Elemental analysis for C₁₈H₂₅NO₄

Calculated: C, 67.69; H, 7.89; N, 4.39.

35 Found: C, 67.54; H, 8.06; N, 4.28.

¹H-NMR(CDCl₃) δ: 0.98 (9H, s), 3.45 (3H, s), 3.58 (1H, t,

$J=6.8$ Hz), 3.75-3.79 (2H, m), 4.14-4.18 (2H, m), 4.23 (2H, bs), 4.90 (2H, bs), 7.44-7.52 (1H, m), 7.63-7.76 (2H, m), 8.40 (1H, dd, $J=0.8$, 8.0 Hz).

(4) 3-Chloromethyl-4-(2-methoxyethoxy)-2-neopentyl-

⁵ 1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))
¹H-NMR(CDCl₃) δ : 0.98 (9H, s), 3.52 (3H, s), 3.76-3.82 (2H, m), 4.11-4.18 (2H, m), 4.21 (2H, bs), 4.96 (2H, bs), 7.50-7.58 (1H, m), 7.67-7.76 (1H, m), 7.87 (1H, dd, $J=0.8$, 8.0 Hz), 8.44 (1H, dd, $J=0.8$, 8.0 Hz).

¹⁰ (5) 2-{4-(2-Methoxyethoxy)-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl}methyl}-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

¹⁵ Melting point 145-146°C.

Elemental analysis for C₂₆H₂₈N₂O₅

Calculated: C, 68.93; H, 6.34; N, 6.18.

Found: C, 69.07; H, 6.06; N, 6.53.

¹H-NMR(CDCl₃) δ : 1.00 (9H, s), 3.47 (3H, s), 3.78-3.82 (2H, m), 4.24-4.29 (2H, m), 4.31 (2H, bs), 5.12 (2H, bs), 7.45-7.54 (1H, m), 7.65-7.92 (6H, m), 8.41 (1H, dd, $J=0.7$, 8.1 Hz).

²⁰ (6) Tert-butyl {4-(2-methoxyethoxy)-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl}methylcarbamate (synthesized according to the method similar to that in Example 1

²⁵ (6))

Melting point 143-144°C.

Elemental analysis for C₂₃H₃₄N₂O₅

Calculated: C, 66.00; H, 8.19; N, 6.69.

³⁰ Found: C, 65.73; H, 8.14; N, 6.78.

¹H-NMR(CDCl₃) δ : 0.99 (9H, s), 1.44 (9H, s), 3.48 (3H, s), 3.74-3.79 (2H, m), 4.07-4.12 (2H, m), 4.19 (2H, bs), 4.61 (2H, d, $J=6.0$ Hz), 5.17 (1H, bs), 7.46-7.54 (1H, m), 7.65-7.73 (1H, m), 7.79 (1H, d, $J=8.2$ Hz), 8.42 (1H, dd, $J=0.7$, 8.2 Hz).

³⁵ (7) 3-(Aminomethyl)-4-(2-methoxyethoxy)-2-neopentyl-

1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 205-206°C.

⁵ Elemental analysis for C₁₈H₂₇N₂O₃Cl 1/4H₂O

Calculated: C, 60.16; H, 7.71; N, 7.80.

Found: C, 59.84; H, 7.52; N, 7.82.

¹H-NMR(DMSO-d₆) δ:0.91 (9H, s), 1.10 (6H, d, J=6.6 Hz), 2.14-2.27 (1H, m), 3.73 (2H, d, J=6.6 Hz), 4.11 (2H, bs),

¹⁰ 4.24 (2H, s), 7.89 (1H, s), 8.38 (1H, s), 8.63 (3H, bs).

Example 50

3-(Aminomethyl)-4-butoxy-7-methyl-2-neopentyl-1(2H)-isoquinolinone hydrochloride

(1) Ethyl 4-hydroxy-7-methyl-2-neopentyl-1-oxo-1,2-

¹⁵ dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (1))

Melting point 90-91°C.

Elemental analysis for C₁₈H₂₃NO₄

Calculated: C, 68.12; H, 7.30; N, 4.41.

²⁰ Found: C, 67.98; H, 7.10; N, 4.22.

¹H-NMR(CDCl₃) δ:0.84 (9H, s), 1.46 (3H, t, J=7.1 Hz), 2.54 (3H, s), 4.42 (2H, bs), 4.49 (2H, q, J=7.1 Hz), 7.57 (1H, dd, J=1.9, 8.0 Hz), 8.04 (1H, d, J=8.0 Hz), 8.26 (1H, d, J=1.9 Hz), 10.90 (1H, s).

²⁵ (2) Ethyl 4-butoxy-7-methyl-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (2))

¹H-NMR(CDCl₃) δ:0.93 (9H, s), 1.00 (3H, t, J=7.3 Hz), 1.44 (3H, t, J=7.0 Hz), 1.47-1.62 (2H, m), 1.73-1.87 (2H, m), 2.51 (3H, s), 3.95 (2H, t, J=6.6 Hz), 4.11 (2H, bs), 4.42 (2H, q, J=7.0 Hz), 7.54 (1H, dd, J=1.7, 8.0 Hz), 7.68 (1H, d, J=8.0 Hz), 8.26 (1H, d, J=1.7 Hz).

(3) 4-Butoxy-7-methyl-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to

³⁵ the method similar to that in Example 4 (3))

Melting point 160.5-161°C.

Elemental analysis for C₂₀H₂₇NO₄

Calculated: C, 69.54; H, 7.88; N, 4.05.

Found: C, 69.45; H, 8.10; N, 3.98.

¹H-NMR(CDCl₃) δ: 0.91 (9H, s), 0.99 (3H, t, J=7.1 Hz),

5 1.44-1.63 (2H, m), 1.76-1.90 (2H, m), 2.50 (3H, s), 4.00 (2H, t, J=6.6 Hz), 4.26 (2H, bs), 5.92 (1H, bs), 7.45-7.56 (2H, m), 8.13 (1H, s).

(4) 4-Butoxy-3-hydroxymethyl-7-methyl-2-neopentyl-1(2H)-isoquinoline (synthesized according to the method

10 similar to that in Example 4 (4))

Melting point 109-110°C.

Elemental analysis for C₂₀H₂₉NO₃

Calculated: C, 72.47; H, 8.82; N, 4.23.

Found: C, 72.18; H, 8.75; N, 4.26.

15 ¹H-NMR(CDCl₃) δ: 0.96 (9H, s), 1.03 (3H, t, J=7.4 Hz), 1.49-1.68 (2H, m), 1.79-1.93 (2H, m), 2.45 (3H, s), 2.61 (1H, bs), 3.90 (2H, t, J=6.6 Hz), 4.22 (2H, bs), 4.87 (2H, bs), 7.43 (1H, dd, J=1.8, 8.0 Hz), 7.56 (1H, d, J=8.0 Hz), 8.09 (1H, d, J=1.8 Hz).

20 (5) 4-Butoxy-3-chloromethyl-7-methyl-2-neopentyl-1(2H)-isoquinoline (synthesized according to the method

similar to that in Example 4 (5))

¹H-NMR(CDCl₃) δ: 0.98 (9H, s), 1.04 (3H, t, J=7.3 Hz), 1.51-1.69 (2H, m), 1.81-1.95 (2H, m), 2.50 (3H, s), 3.95 (2H, t, J=6.4 Hz), 4.18 (2H, bs), 4.90 (2H, bs), 7.52 (1H, dd, J=1.8, 8.1 Hz), 7.65 (1H, d, J=8.1 Hz), 8.24 (1H, d, J=1.8 Hz).

(6) 2-{(4-Butoxy-7-methyl-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl}-1H-isoindole-1,3(2H)-dione

30 (synthesized according to the method similar to that in Example 4 (6))

Melting point 174-175°C.

Elemental analysis for C₂₈H₃₂N₂O₄ 1/4H₂O

Calculated: C, 72.31; H, 7.04; N, 6.02.

35 Found: C, 72.57; H, 7.35; N, 6.04.

¹H-NMR(CDCl₃) δ: 1.00 (9H, s), 1.01 (3H, t, J=7.3 Hz),

1.44-1.59 (2H, m), 1.81-1.95 (2H, m), 2.48 (3H, s), 4.02 (2H, t, J=6.8 Hz), 4.10 (2H, bs), 5.08 (2H, s), 7.50 (1H, dd, J=1.7, 8.3 Hz), 7.63-7.82 (5H, m), 8.22 (1H, d, J=1.7 Hz).

- ⁵ (7) Tert-butyl (4-butoxy-7-methyl-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 1 (6))

Melting point 153-154°C.

- ¹⁰ Elemental analysis for C₂₅H₃₈N₂O₄

Calculated: C, 69.74; H, 8.90; N, 6.51.

Found: C, 69.65; H, 9.13; N, 6.56.

¹H-NMR(CDCl₃) δ:0.99 (9H, s), 1.03 (3H, t, J=7.2 Hz), 1.45 (9H, s), 1.52-1.63 (2H, m), 1.79-1.93 (2H, m), 2.49

- ¹⁵ (3H, s), 3.86 (2H, t, J=6.5 Hz), 4.18 (2H, bs), 4.56 (2H, t, J=5.4 Hz), 4.68 (1H, bs), 7.50 (1H, dd, J=1.8, 8.0 Hz), 7.60 (1H, d, J=8.0 Hz), 8.21 (1H, d, J=1.8 Hz).

(8) 3-(Aminomethyl)-4-butoxy-7-methyl-2-neopentyl-1(2H)-isoquinolinone hydrochloride (synthesized according to

- ²⁰ the method similar to that in Example 1 (7))

Melting point 231-233°C.

Elemental analysis for C₂₀H₃₁N₂O₂Cl

Calculated: C, 65.47; H, 8.52; N, 7.63..

Found: C, 65.44; H, 8.53; N, 7.86.

- ²⁵ ¹H-NMR(DMSO-d₆) δ:0.99 (9H, s), 0.99 (3H, t, J=7.2 Hz), 1.45-1.64 (2H, m), 1.77-1.91 (2H, m), 2.47 (3H, s), 3.92 (2H, t, J=6.6 Hz), 4.10 (2H, bs), 4.23 (2H, d, J=5.2 Hz), 7.63-7.72 (2H, m), 8.09 (1H, s), 8.56 (3H, bs)..

Example 51

- ³⁰ 3-(Aminomethyl)-4-butoxy-6-methyl-2-neopentyl-1(2H)-isoquinolinone hydrochloride

(1) Ethyl 4-hydroxy-6-methyl-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (1))

- ³⁵ ¹H-NMR(CDCl₃) δ:0.84 (9H, s), 1.46 (3H, t, J=7.2 Hz), 2.54 (3H, s), 4.42 (2H, bs), 4.47 (2H, q, J=7.2 Hz),

7.51 (1H, dd, J=1.9, 8.0 Hz), 7.93 (1H, d, J=1.9 Hz),
8.33 (1H, d, J=8.0 Hz), 10.86 (1H, s).

(2) Ethyl 4-butoxy-6-methyl-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according

⁵ to the method similar to that in Example 1 (2))

¹H-NMR(CDCl₃) δ: 0.94 (9H, s), 1.00 (3H, t, J=7.2 Hz),
1.44 (3H, t, J=7.2 Hz), 1.47-1.60 (2H, m), 1.74-1.91 (2H,
m), 2.52 (3H, s), 3.96 (2H, t, J=6.4 Hz), 4.07 (2H, bs),
4.43 (2H, q, J=7.2 Hz), 7.38 (1H, dd, J=1.0, 8.0 Hz),

¹⁰ 7.68 (1H, d, J=1.0 Hz), 8.26 (1H, d, J=8.0 Hz).

(3) 4-Butoxy-6-methyl-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to
the method similar to that in Example 4 (3))

Melting point 153-154°C.

¹⁵ Elemental analysis for C₂₀H₂₇NO₄

Calculated: C, 69.54; H, 7.88; N, 4.05.

Found: C, 69.59; H, 8.16; N, 4.06.

¹H-NMR(CDCl₃) δ: 0.91 (9H, s), 1.01 (3H, t, J=7.1 Hz),
1.48-1.65 (2H, m), 1.77-1.88 (2H, m), 2.52 (3H, s), 4.02
²⁰ (2H, t, J=6.4 Hz), 4.22 (2H, bs), 6.42 (1H, bs), 7.38
(1H, dd, J=1.3, 8.2 Hz), 7.45 (1H, d, J=1.3 Hz), 8.25
(1H, d, J=8.2 Hz).

(4) 4-Butoxy-3-hydroxymethyl-6-methyl-2-neopentyl-1(2H)-isoquinolinone (synthesized according to the method

²⁵ similar to that in Example 4 (4))

Melting point 133-134°C.

Elemental analysis for C₂₀H₂₉NO₃

Calculated: C, 72.47; H, 8.82; N, 4.23.

Found: C, 72.43; H, 8.80; N, 4.24.

³⁰ ¹H-NMR(CDCl₃) δ: 0.97 (9H, s), 1.04 (3H, t, J=7.2 Hz),
1.51-1.69 (2H, m), 1.80-1.94 (2H, m), 2.38 (1H, bs),
2.49 (3H, s), 3.90 (2H, t, J=6.6 Hz), 4.20 (2H, bs),
4.86 (2H, bs), 7.27 (1H, dd, J=1.6, 8.0 Hz), 7.45 (1H, d,
J=1.6 Hz), 8.22 (1H, d, J=8.0 Hz).

³⁵ (5) 4-Butoxy-3-chloromethyl-6-methyl-2-neopentyl-1(2H)-isoquinolinone (synthesized according to the method

similar to that in Example 4 (5))

¹H-NMR(CDCl₃) δ: 0.98 (9H, s), 1.05 (3H, t, J=7.1 Hz), 1.56-1.71 (2H, m), 1.82-1.92 (2H, m), 2.52 (3H, s), 3.95 (2H, t, J=6.5 Hz), 4.14 (2H, bs), 4.88 (2H, bs), 7.35

5 (1H, dd, J=1.8, 8.0 Hz), 7.51 (1H, d, J=1.8 Hz), 8.32 (1H, d, J=8.0 Hz).

(6) 2-{(4-Butoxy-6-methyl-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl}-1H-isoindole-1,3(2H)-dione

(synthesized according to the method similar to that in

10 Example 4 (6))

Melting point 170-172°C.

Elemental analysis for C₂₈H₃₂N₂O₄

Calculated: C, 73.02; H, 7.00; N, 6.08.

Found: C, 72.72; H, 7.05; N, 6.25.

15 ¹H-NMR(CDCl₃) δ: 1.00 (9H, s), 1.01 (3H, t, J=7.2 Hz), 1.50-1.65 (2H, m), 1.82-1.93 (2H, m), 2.50 (3H, s), 4.03 (2H, t, J=6.8 Hz), 4.06 (2H, bs), 5.08 (2H, s), 7.31 (1H, dd, J=1.4, 8.2 Hz), 7.53 (1H, d, J=1.4 Hz), 7.68-7.82 (4H, m), 8.29 (1H, d, J=8.2 Hz).

20 (7) Tert-butyl (4-butoxy-6-methyl-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 1 (6))

Melting point 127-129°C.

25 Elemental analysis for C₂₅H₃₈N₂O₄

Calculated: C, 69.74; H, 8.90; N, 6.51.

Found: C, 69.80; H, 8.75; N, 6.46.

¹H-NMR(CDCl₃) δ: 0.99 (9H, s), 1.00 (3H, t, J=7.6 Hz), 1.45 (9H, s), 1.53-1.68 (2H, m), 1.75-1.94 (2H, m), 2.51

30 (3H, s), 3.87 (2H, t, J=6.6 Hz), 4.14 (2H, bs), 4.56 (2H, d, J=5.2 Hz), 4.65 (1H, bs), 7.32 (1H, dd, J=1.4, 8.4 Hz), 7.47 (1H, d, J=1.4 Hz), 8.30 (1H, d, J=8.4 Hz).

(8) 3-(Aminomethyl)-4-butoxy-6-methyl-2-neopentyl-1(2H)-isoquinolinone hydrochloride (synthesized according to

35 the method similar to that in Example 1 (7))

Melting point 201-203°C.

Elemental analysis for C₂₀H₃₁N₂O₂Cl

Calculated: C, 65.47; H, 8.52; N, 7.63.

Found: C, 65.50; H, 8.59; N, 7.56.

¹H-NMR(DMSO-d₆) δ: 0.90 (9H, s), 1.00 (3H, t, J=7.3 Hz),

5 1.50-1.65 (2H, m), 1.78-1.91 (2H, m), 2.50 (3H, s), 3.93 (2H, t, J=6.2 Hz), 4.09 (2H, bs), 4.23 (2H, bs), 7.31 (1H, d, J=8.0 Hz), 7.55 (1H, s), 8.16 (1H, d, J=8.0 Hz), 8.58 (3H, bs).

Example 52

10 3-(Aminomethyl)-4-butoxy-2-neopentyl-7-trifluoromethyl-1(2H)-isoquinolinone hydrochloride

(1) Ethyl 4-hydroxy-2-neopentyl-1-oxo-7-trifluoromethyl-1,2-dihydro-3-isooquinolinecarboxylate (synthesized according to the method similar to that in Example 1

15: (1))

Melting point 133.5-134°C.

Elemental analysis for C₁₈H₂₀NO₄F₃

Calculated: C, 58.22; H, 5.43; N, 3.77.

Found: C, 58.24; H, 5.48; N, 3.76.

20 ¹H-NMR(CDCl₃) δ: 0.86 (9H, s), 1.48 (3H, t, J=7.2 Hz), 4.45 (2H, bs), 4.50 (2H, q, J=7.2 Hz), 7.96 (1H, dd, J=1.8, 8.4 Hz); 8.27 (1H, d, J=8.4 Hz), 8.75 (1H, d, J=1.8 Hz), 10.71 (1H, s).

(2) Ethyl 4-butoxy-2-neopentyl-1-oxo-7-trifluoromethyl-1,2-dihydro-3-isooquinolinecarboxylate (synthesized according to the method similar to that in Example 1

(2))

25 ¹H-NMR(CDCl₃) δ: 0.95 (9H, s), 1.01 (3H, t, J=7.3 Hz), 1.45 (3H, t, J=7.1 Hz), 1.52-1.63 (2H, m), 1.74-1.88 (2H, m), 3.96 (2H, t, J=6.6 Hz), 4.09 (2H, bs), 4.45 (2H, q, J=7.1 Hz), 7.90-7.94 (2H, m), 8.73-8.75 (1H, m).

30 (3) 4-Butoxy-2-neopentyl-1-oxo-7-trifluoromethyl-1,2-dihydro-3-isooquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4

35 (3))

Melting point 169-170°C.

Elemental analysis for $C_{20}H_{24}NO_4F_3$

Calculated: C, 60.14; H, 6.06; N, 3.51.

Found: C, 60.17; H, 5.94; N, 3.45.

1H -NMR(CDCl₃) δ : 0.95 (9H, s), 1.00 (3H, t, J=7.4 Hz),

5 1.45-1.64 (2H, m), 1.78-1.92 (2H, m), 4.03 (2H, t, J=6.6 Hz), 4.26 (2H, bs), 5.02 (1H, bs), 7.84-7.95 (2H, m), 8.70 (1H, s).

(4) 4-Butoxy-3-hydroxymethyl-2-neopentyl-7-trifluoromethyl-1(2H)-isoquinolinone (synthesized

10 according to the method similar to that in Example 4 (4))

Melting point 98-99°C.

Elemental analysis for $C_{20}H_{26}NO_3F_3$ 1/4H₂O

Calculated: C, 61.31; H, 6.85; N, 3.59.

15 Found: C, 61.54; H, 6.83; N, 3.79.

1H -NMR(CDCl₃) δ : 0.95 (9H, s), 1.05 (3H, t, J=7.3 Hz), 1.51-1.70 (2H, m), 1.81-1.95 (2H, m), 3.02 (1H, bs), 3.91 (2H, t, J=6.4 Hz), 4.25 (2H, bs), 4.89 (2H, bs), 7.70-7.75 (2H, m), 8.45 (1H, s).

20 (5) 4-Butoxy-3-chloromethyl-2-neopentyl-7-trifluoromethyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

1H -NMR(CDCl₃) δ : 0.99 (9H, s), 1.04 (3H, t, J=7.4 Hz),

25 1.52-1.76 (2H, m), 1.82-1.96 (2H, m), 3.95 (2H, t, J=6.4 Hz), 4.22 (2H, bs), 4.89 (2H, bs), 7.83-7.93 (2H, m), 8.72-8.74 (1H, m).

(6) 2-{(4-Butoxy-2-neopentyl-1-oxo-7-trifluoromethyl-1,2-dihydro-3-isooquinolinyl)methyl}-1H-isocindole-

30 1,3(2H)-dione (synthesized according to the method

similar to that in Example 4 (6))

Melting point 132-133°C.

Elemental analysis for $C_{28}H_{29}N_2O_4F_3$

Calculated: C, 65.36; H, 5.68; N, 5.44.

35 Found: C, 65.34; H, 5.38; N, 5.49.

1H -NMR(CDCl₃) δ : 1.01 (3H, t, J=7.3 Hz), 1.02 (9H, s),

1.46-1.62 (2H, m), 1.82-1.93 (2H, m), 4.02 (2H, t, J=6.8 Hz), 4.05 (2H, bs), 5.09 (2H, s), 7.70-7.86 (6H, m), 8.70 (1H, s).

(7) Tert-butyl (4-butoxy-2-neopentyl-1-oxo-7-trifluoromethyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 1 (6))

Elemental analysis for C₂₅H₃₅N₂O₄F₃

Calculated: C, 61.97; H, 7.28; N, 5.78.

10 Found: C, 61.86; H, 7.38; N, 5.73.

¹H-NMR(CDCl₃) δ:1.00 (9H, s), 1.04 (3H, t, J=7.4 Hz), 1.46 (9H, s), 1.53-1.68 (2H, m), 1.81-1.95 (2H, m), 3.87 (2H, t, J=6.6 Hz), 4.14 (2H, bs), 4.59 (2H, d, J=5.0 Hz), 4.82 (1H, bs), 7.77-7.88 (2H, m), 8.66 (1H, d, J=0.6 Hz).

15 (8) 3-(Aminomethyl)-4-butoxy-2-neopentyl-7-trifluoromethyl-1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 224-225°C.

20 Elemental analysis for C₂₀H₂₈N₂O₂ClF₃

Calculated: C, 57.07; H, 6.71; N, 6.66.

Found: C, 56.77; H, 6.69; N, 6.73.

¹H-NMR(DMSO-d₆) δ:0.92 (9H, s), 1.00 (3H, t, J=7.3 Hz), 1.50-1.61 (2H, m), 1.80-1.92 (2H, m), 3.96 (2H, t, J=6.4 Hz), 4.15 (2H, bs), 4.29 (2H, bs), 8.00 (1H, d, J=8.4 Hz), 8.17 (1H, dd, J=1.8, 8.4 Hz), 8.52 (1H, d, J=1.8 Hz), 8.66 (3H, bs).

Example 53

3-(Aminomethyl)-4-butoxy-2-neopentyl-6-trifluoromethyl-1(2H)-isoquinolinone hydrochloride

(1) Ethyl 4-hydroxy-2-neopentyl-1-oxo-6-trifluoromethyl-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (1))

35 ¹H-NMR(CDCl₃) δ:0.86 (9H, s), 1.49 (3H, t, J=7.2 Hz), 4.46 (2H, bs), 4.51 (2H, q, J=7.2 Hz), 7.89 (1H, dd,

$J=2.0, 8.4$ Hz), 8.43 (1H, d, $J=2.0$ Hz), 8.57 (1H, d, $J=8.4$ Hz), 10.79 (1H, s).

(2) Ethyl 4-butoxy-2-neopentyl-1-oxo-6-trifluoromethyl-1,2-dihydro-3-isoquinolinecarboxylate (synthesized

5 according to the method similar to that in Example 1
(2))

$^1\text{H-NMR}(\text{CDCl}_3)$ δ : 0.95 (9H, s), 1.02 (3H, t, $J=7.4$ Hz),
1.45 (3H, t, $J=7.1$ Hz), 1.49-1.66 (2H, m), 1.76-1.90 (2H,
m), 3.98 (2H, t, $J=6.4$ Hz), 4.11 (2H, bs), 4.46 (2H, q,
10 $J=7.1$ Hz), 7.78 (1H, dd, $J=1.6, 8.4$ Hz), 8.05 (1H, d,
 $J=1.6$ Hz), 8.57 (1H, d, $J=8.4$ Hz).

(3) 4-Butoxy-2-neopentyl-1-oxo-6-trifluoromethyl-1,2-dihydro-3-isoquinolinic acid (synthesized
according to the method similar to that in Example 4

15 (3))

Melting point 164-166°C.

Elemental analysis for $\text{C}_{20}\text{H}_{24}\text{NO}_4\text{F}_3$

Calculated: C, 60.14; H, 6.06; N, 3.51.

Found: C, 60.15; H, 5.86; N, 3.43.

20 $^1\text{H-NMR}(\text{CDCl}_3)$ δ : 0.95 (9H, s), 1.01 (3H, t, $J=7.2$ Hz),
1.48-1.66 (2H, m), 1.78-1.92 (2H, m), 4.04 (2H, t, $J=6.4$ Hz),
4.28 (2H, bs), 5.01 (1H, bs), 7.79 (1H, dd, $J=1.4,$
8.6 Hz), 8.00 (1H, d, $J=1.4$ Hz), 8.54 (1H, d, $J=8.6$ Hz).

(4) 4-Butoxy-3-hydroxymethyl-2-neopentyl-6-
25 trifluoromethyl-1(2H)-isoquinolinone (synthesized
according to the method similar to that in Example 4
(4))

Melting point 107-108°C.

Elemental analysis for $\text{C}_{20}\text{H}_{26}\text{NO}_3\text{F}_3$

30 Calculated: C, 62.33; H, 6.80; N, 3.63.

Found: C, 62.31; H, 6.74; N, 3.74.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ : 0.97 (9H, s), 1.08 (3H, t, $J=6.9$ Hz),
1.52-1.71 (2H, m), 1.81-1.95 (2H, m), 2.48 (1H, bs),
3.91 (2H, t, $J=6.4$ Hz), 4.23 (2H, bs), 4.89 (2H, bs),

35 7.63 (1H, d, $J=8.5$ Hz), 7.94 (1H, s), 8.42 (1H, d, $J=8.5$ Hz).

(5) 4-Butoxy-3-chloromethyl-2-neopentyl-6-trifluoromethyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

⁵ ¹H-NMR(CDCl₃) δ: 0.99 (9H, s), 1.05 (3H, t, J=7.3 Hz), 1.54-1.72 (2H, m), 1.83-1.97 (2H, m), 3.96 (2H, t, J=6.4 Hz), 4.22 (2H, bs), 4.89 (2H, bs), 7.74 (1H, dd, J=1.6, 8.6 Hz), 8.02 (1H, d, J=1.6 Hz), 8.55 (1H, d, J=8.6 Hz).

¹⁰ (6) 2-{(4-Butoxy-2-neopentyl-1-oxo-6-trifluoromethyl-1,2-dihydro-3-isoquinolinyl)methyl}-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))
Melting point 123-124°C.

Elemental analysis for C₂₈H₂₉N₂O₄F₃

¹⁵ Calculated: C, 65.36; H, 5.68; N, 5.44.

Found: C, 65.44; H, 5.77; N, 5.48.

¹H-NMR(CDCl₃) δ: 1.01 (9H, s), 1.02 (3H, t, J=7.3 Hz), 1.48-1.67 (2H, m), 1.83-1.97 (2H, m), 4.04 (2H, t, J=6.6 Hz), 4.07 (2H, bs), 5.09 (2H, s), 7.67-7.84 (5H, m), 8.03 (1H, s), 8.52 (1H, d, J=8.4 Hz).

²⁰ (7) Tert-butyl (4-butoxy-2-neopentyl-1-oxo-6-trifluoromethyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 1 (6))
Melting point 153-154°C.

Elemental analysis for C₂₅H₃₅N₂O₄F₃

Calculated: C, 61.97; H, 7.28; N, 5.78.

Found: C, 61.71; H, 7.09; N, 5.75.

¹H-NMR(CDCl₃) δ: 1.00 (9H, s), 1.04 (3H, t, J=7.4 Hz), 1.45 (9H, s), 1.51-1.70 (2H, m), 1.81-1.95 (2H, m), 3.88 (2H, t, J=6.4 Hz), 4.14 (2H, bs), 4.59 (2H, d, J=5.8 Hz), 4.73 (1H, bs), 7.69 (1H, dd, J=1.6, 8.2 Hz), 7.96 (1H, d, J=1.6 Hz), 8.52 (1H, d, J=8.2 Hz).

³⁰ (8) 3-(Aminomethyl)-4-butoxy-2-neopentyl-6-trifluoromethyl-1(2H)-isoquinolinone hydrochloride
(synthesized according to the method similar to that in

Example 1 (7))

Melting point 206-208°C.

Elemental analysis for $C_{20}H_{28}N_2O_2ClF_3$ 1/2H₂O

Calculated: C, 55.88; H, 6.80; N, 6.52.

⁵ Found: C, 55.71; H, 6.58; N, 6.19.

¹H-NMR(DMSO-d₆) δ:0.92 (9H, s), 1.00 (3H, t, J=7.4 Hz), 1.52-1.64 (2H, m), 1.78-1.92 (2H, m), 3.97 (2H, t, J=6.5 Hz), 4.14 (2H, bs), 4.29 (2H, bs), 7.94 (1H, d, J=8.6 Hz), 8.00 (1H, s), 8.49 (1H, d, J=8.6 Hz), 8.61 (3H, bs).

10 Example 54

Methyl 3-{2-[3-(aminomethyl)-4-butoxy-6,7-dichloro-1-oxo-2(1H)-isoquinolinyl]ethylcarbamate hydrochloride

(1) A solution of 3-[4-butoxy-6,7-dichloro-3-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-1-oxo-2(1H)-

¹⁵ isoquinolinyl]propionic acid (0.78 g, 1.5 mmol);

diphenylphosphoryl azide (0.39 ml, 1.8 mmol) and

triethylamine (0.25 ml, 1.8 mmol) in N,N-

dimethylformamide (10 ml) was stirred at room

temperature for 2 h. The reaction mixture was poured

²⁰ into water and extracted with ethyl acetate. The

extract was washed with brine, dried over anhydrous

magnesium sulfate and concentrated under reduced

pressure. The residue was dissolved in toluene (20 ml)

and the mixture was refluxed with stirring. To the

²⁵ obtained mixture was added methanol (1 ml) and the

mixture was refluxed with stirring for 1 h. The

reaction mixture was poured into water and extracted

with ethyl acetate. The extract was washed with brine,

dried over anhydrous magnesium sulfate and concentrated

³⁰ under reduced pressure. The residue was recrystallized

from tetrahydrofuran - diisopropyl ether to give methyl

2-[4-butoxy-6,7-dichloro-3-[(1,3-dioxo-1,3-dihydro-2H-

isoindol-2-yl)methyl]-1-oxo-2(1H)-

isoquinolinyl]ethylcarbamate (0.30 g, 36.6%) as crystals.

³⁵ Melting point 241-243°C.

¹H-NMR(CDCl₃) δ:0.99 (3H, t, J=7.3 Hz), 1.43-1.58 (2H,

m), 1.72-1.91 (2H, m), 3.51(2H, q, J=6.6 Hz), 3.61 (3H, s), 3.91 (2H, t, J=6.8 Hz), 4.45 (2H, t, J=6.6 Hz), 5.07 (2H, s), 5.47 (1H, bs), 7.71-7.88 (5H, m), 8.47 (1H, s).

(2) Methyl 2-{4-butoxy-3-{{(tert-

⁵ butoxycarbonyl}amino)methyl}-6,7-dichloro-1-oxo-2(1H)-isoquinolinyl}ethylcarbamate (synthesized according to the method similar to that in Example 1 (6))

Melting point 185.5-186°C.

Elemental analysis for C₂₃H₃₁N₃O₆Cl₂

¹⁰ Calculated: C, 53.49; H, 6.05; N, 8.14.

Found: C, 53.64; H, 6.11; N, 8.30.

¹H-NMR(CDCl₃) δ:1.04 (3H, t, J=7.3 Hz), 1.46 (9H, s), 1.52-1.67 (2H, m), 1.80-1.94 (2H, m), 3.54 (2H, t, J=6.2 Hz), 3.59 (3H, s), 3.85 (2H, t, J=6.5 Hz), 4.29 (2H, t, ¹⁵J=6.2 Hz), 4.52 (2H, d, J=5.8 Hz), 5.34 (1H, s), 5.51 (1H, bs), 7.78 (1H, s), 8.46 (1H, s).

(3) Methyl 3-{2-{3-(aminomethyl)-4-butoxy-6,7-dichloro-1-oxo-2(1H)-isoquinolinyl}ethylcarbamate hydrochloride (synthesized according to the method similar to that in

²⁰ Example 1 (7))

Melting point 230-231°C.

Elemental analysis for C₁₈H₂₄N₃O₄Cl₃

Calculated: C, 47.75; H, 5.34; N, 9.28.

Found: C, 47.47; H, 5.47; N, 9.10.

²⁵ ¹H-NMR(DMSO-d₆) δ:0.99 (3H, t, J=7.3 Hz), 1.45-1.63 (2H, m), 1.76-1.91 (2H, m), 3.29 (2H, q, J=6.4 Hz), 3.47 (3H, s), 3.91 (2H, t, J=6.4 Hz), 4.12 (2H, t, J=6.4 Hz), 4.23 (2H, d, J=4.4 Hz), 7.44 (1H, bs), 7.93 (1H, s), 8.39 (1H, s), 8.72 (3H, bs).

³⁰ Example 55

N-{2-{3-(Aminomethyl)-4-butoxy-6,7-dichloro-1-oxo-2(1H)-isoquinolinyl}ethyl}-1-pyrrolidinecarboxamide hydrochloride

(1) N-{2-{4-Butoxy-6,7-dichloro-3-[(1,3-dioxo-1,3-

³⁵ dihydro-2H-isoindol-2-yl)methyl]-1-oxo-2(1H)-isoquinolinyl}ethyl}-1-pyrrolidinecarboxamide

(synthesized according to the method similar to that in Example 4 (6))

Melting point 197-198°C.

Elemental analysis for $C_{29}H_{30}N_4O_5Cl_2 \cdot 1/2H_2O$

⁵ Calculated: C, 58.59; H, 5.26; N, 9.42.

Found: C, 58.58; H, 5.54; N, 9.32.

¹H-NMR(CDCl₃) δ: 0.98 (3H, t, J=7.3 Hz), 1.38-1.57 (2H, m), 1.76-1.89 (6H, m), 3.23-3.30 (4H, m), 3.56 (2H, q, J=6.6 Hz), 3.89 (2H, t, J=6.8 Hz), 4.53 (2H, t, J=6.6

¹⁰ Hz), 5.08 (1H, bs), 5.12 (2H, s), 7.70-7.85 (5H, m), 8.47 (1H, s).

(2) Tert-butyl {4-butoxy-6,7-dichloro-1-oxo-2-{2-(1-pyrrolidinylcarbonyl)amino}ethyl}-1,2-dihydro-3-isoquinolinylmethylcarbamate (synthesized according to

¹⁵ the method similar to that in Example 1 (6)).

Melting point 161-162°C.

Elemental analysis for $C_{26}H_{36}N_4O_5Cl_2$

Calculated: C, 56.22; H, 6.53; N, 10.09.

Found: C, 56.61; H, 6.24; N, 9.99.

²⁰ ¹H-NMR(CDCl₃) δ: 1.03 (3H, t, J=7.3 Hz), 1.45 (9H, s), 1.52-1.66 (2H, m), 1.80-1.91 (8H, m), 3.17-3.24 (4H, m), 3.61 (2H, q, J=6.3 Hz), 3.88 (2H, t, J=6.6 Hz), 4.32 (2H, t, J=6.3 Hz), 4.53 (2H, d, J=6.0 Hz), 5.09 (1H, bs), 6.07 (1H, bs), 7.81 (1H, s), 8.44 (1H, s).

²⁵ (3) N-{2-{3-(Aminomethyl)-4-butoxy-6,7-dichloro-1-oxo-2(1H)-isoquinolinyl}ethyl}-1-pyrrolidinecarboxylic acid hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 190-192°C.

³⁰ Elemental analysis for $C_{21}H_{29}N_4O_3Cl_3 \cdot 3/2H_2O$

Calculated: C, 48.61; H, 6.17; N, 10.80.

Found: C, 48.85; H, 6.06; N, 10.81.

¹H-NMR(DMSO-d₆) δ: 0.99 (3H, t, J=7.3 Hz), 1.48-1.63 (2H, m), 1.79-1.91 (6H, m), 3.16-3.28 (6H, m), 3.92 (2H, t,

³⁵ J=6.4 Hz), 4.09 (2H, t, J=6.8 Hz), 4.31 (2H, bs), 6.80 (1H, bs), 7.92 (1H, s), 8.38 (1H, s), 8.95 (3H, bs).

Example 56

3-(Aminomethyl)-4-butoxy-2-neopentylbenzo{g}isoquinolin-1(2H)-one hydrochloride

(1) Ethyl 4-hydroxy-2-neopentyl-1-oxo-1,2-dihydrobenzo{g}isoquinoline-3-carboxylate (synthesized according to the method similar to that in Example 1 (1))

Melting point 140-141.5°C.

Elemental analysis for $C_{21}H_{23}NO_4$

Calculated: C, 71.37; H, 6.56; N, 3.96.

Found: C, 71.08; H, 6.36; N, 3.72.

1H -NMR(CDCl₃) δ: 0.87 (9H, s), 1.48 (3H, t, J=7.2 Hz), 4.50 (2H, q, J=7.2 Hz), 4.55 (2H, bs), 7.59-7.69 (2H, m), 8.05-8.12 (2H, m), 8.67 (1H, s), 9.03 (1H, s), 11.11 (1H, s).

(2) Ethyl 4-butoxy-2-neopentyl-1-oxo-1,2-dihydrobenzo{g}isoquinoline-3-carboxylate (synthesized according to the method similar to that in Example 1)

(2)

1H -NMR(CDCl₃) δ: 0.96 (9H, s), 1.05 (3H, t, J=7.3 Hz), 1.48 (3H, t, J=7.1 Hz), 1.55-1.66 (2H, m), 1.74-1.95 (2H, m), 4.06 (2H, t, J=6.4 Hz), 4.11 (2H, bs), 4.46 (2H, q, J=7.1 Hz), 7.52-7.67 (2H, m), 7.98-8.09 (2H, m), 8.24 (1H, s), 9.05 (1H, s).

(3) 4-Butoxy-2-neopentyl-1-oxo-1,2-dihydrobenzo{g}isoquinoline-3-carboxylic acid (synthesized according to the method similar to that in Example 4 (3)).

Melting point 203-205°C.

Elemental analysis for $C_{23}H_{27}NO_4$

Calculated: C, 72.42; H, 7.13; N, 3.67.

Found: C, 72.39; H, 7.05; N, 3.53.

1H -NMR(CDCl₃) δ: 0.94 (9H, s), 1.03 (3H, t, J=7.1 Hz), 1.48-1.66 (2H, m), 1.79-1.93 (2H, m), 4.06 (2H, t, J=6.6 Hz), 4.28 (2H, bs), 7.55-7.67 (2H, m), 7.74-7.82 (2H, m), 8.03-8.08 (1H, m), 8.89 (1H, s).

(4) 4-Butoxy-3-hydroxymethyl-2-neopentyl-

benzo{g}isoquinolin-1(2H)-one (synthesized according to the method similar to that in Example 4 (4))
Melting point 147-148°C.

Elemental analysis for C₂₃H₂₉NO₃

⁵ Calculated: C, 75.17; H, 7.95; N, 3.81.

Found: C, 75.12; H, 8.10; N, 3.65.

¹H-NMR(CDCl₃) δ:0.98 (9H, s), 1.08 (3H, t, J=7.3 Hz), 1.56-1.75 (2H, m), 1.86-1.99 (2H, m), 2.73 (1H, bs), 3.97 (2H, t, J=6.6 Hz), 4.25 (2H, bs), 4.92 (2H, bs),

¹⁰ 7.45-7.57 (2H, m), 7.76-7.80 (1H, m), 7.91 (1H, s), 7.94-7.99 (1H, m), 8.85 (1H, s).

(5) 4-Butoxy-3-chloromethyl-2-neopentyl-benzo{g}isoquinolin-1(2H)-one (synthesized according to the method similar to that in Example 4 (5))

¹⁵ ¹H-NMR(CDCl₃) δ:1.00 (9H, s), 1.08 (3H, t, J=7.2 Hz), 1.57-1.76 (2H, m), 1.89-2.02 (2H, m), 4.05 (2H, t, J=6.5 Hz), 4.21 (2H, bs), 4.95 (2H, bs), 7.50-7.66 (2H, m), 7.98-8.09 (2H, m), 8.20 (1H, s), 9.04 (1H, s).

(6) 2-{(4-Butoxy-2-neopentyl-1-oxo-1,2-dihydrobenzo{g}-isoquinolin-3-yl)methyl}-1H-isoindole-1,3(2H)-dione
(synthesized according to the method similar to that in Example 4 (6))

Melting point 244-245°C.

Elemental analysis for C₃₁H₃₂N₂O₄

²⁵ Calculated: C, 74.98; H, 6.50; N, 5.64.

Found: C, 74.73; H, 6.58; N, 5.60.

¹H-NMR(CDCl₃) δ:1.02 (9H, s), 1.05 (3H, t, J=7.2 Hz), 1.53-1.71 (2H, m), 1.90-2.04 (2H, m), 4.12 (2H, bs), 4.15 (2H, t, J=6.8 Hz), 5.14 (2H, s), 7.48-7.64 (2H, m),

³⁰ 7.68-7.83 (4H, m), 7.96-8.06 (2H, m), 8.21 (1H, s), 9.01 (1H, s).

(7) Tert-butyl (4-butoxy-2-neopentyl-1-oxo-1,2-dihydrobenzo{g}isoquinolin-3-yl)methylcarbamate
(synthesized according to the method similar to that in Example 1 (6))

¹H-NMR(CDCl₃) δ:1.01 (9H, s), 1.07 (3H, t, J=7.3 Hz),

1.47 (9H, s), 1.50-1.73 (2H, m), 1.87-2.01 (2H, m), 3.96 (2H, t, J=6.4 Hz), 4.14 (2H, bs), 4.62 (2H, d, J=5.2 Hz), 4.73 (1H, bs), 7.48-7.64 (2H, m), 7.94-8.06 (2H, m), 8.11 (1H, s), 9.00 (1H, s).

⁵ (8) 3-(Aminomethyl)-4-butoxy-2-neopentylbenzo{g}isoquinolin-1(2H)-one hydrochloride (synthesized according to the method similar to that in Example 1 (7))
Melting point 231-232°C.

¹⁰ Elemental analysis for C₂₃H₃₁N₂O₂Cl
Calculated: C, 68.55; H, 7.55; N, 6.95.
Found: C, 68.30; H, 7.80; N, 7.02.

¹¹ ¹H-NMR(DMSO-d₆) δ:0.93 (9H, s), 1.04 (3H, t, J=7.1 Hz), 1.56-1.67 (2H, m), 1.90-1.97 (2H, m), 4.05 (2H, bs),
¹⁵ 4.14 (2H, bs), 4.30 (2H, bs), 7.64-7.75 (2H, m), 8.19-8.27 (2H, m), 8.32 (1H, s), 8.63 (3H, bs), 8.99 (1H, s).

Example 57

3-(Aminomethyl)-4-butoxy-6-methoxy-2-neopentyl-1(2H)-isoquinolinone hydrochloride

²⁰ (1) Tert-butyl 4-hydroxy-2-neopentyl-6-fluoro-1-oxo-1,2-dihydro-3-isoquinoline-3-carboxylate (synthesized according to the method similar to that in Example 1 (1))
Melting point 130-131°C.

²⁵ Elemental analysis for C₁₉H₂₄NO₄F
Calculated: C, 65.31; H, 6.92; N, 4.01.
Found: C, 65.32; H, 7.19; N, 3.92..

¹H-NMR(CDCl₃) δ:0.86 (9H, s), 1.65 (9H, s), 4.51 (2H, bs), 7.30-7.40 (1H, m), 7.74 (1H, dd, J=2.6, 9.0 Hz),
³⁰ 8.46 (1H, dd, J=5.4, 9.0 Hz), 10.68 (1H, s).

(2) Tert-butyl 4-butoxy-2-neopentyl-6-fluoro-1-oxo-1,2-dihydro-3-isoquinoline-3-carboxylate (synthesized according to the method similar to that in Example 1 (2))

³⁵ ¹H-NMR(CDCl₃) δ:0.97 (9H, s), 1.01 (3H, t, J=6.8 Hz), 1.49-1.60 (2H, m), 1.63 (9H, s), 1.73-1.86 (2H, m), 3.96

(2H, t, J=6.6 Hz), 4.00 (2H, bs), 7.18-7.27 (1H, m), 7.35 (1H, dd, J=2.4, 9.4 Hz), 8.43 (1H, dd, J=5.4, 8.8 Hz).

(3) A solution of tert-butyl 4-butoxy-2-neopentyl-6-fluoro-1-oxo-1,2-dihydro-3-isoquinoline-3-carboxylate (6.08 g, 15 mmol) in trifluoroacetic acid (20 ml) was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the residue was recrystallized from ethyl acetate - n-hexane to give 4-butoxy-2-neopentyl-6-fluoro-1-oxo-1,2-dihydro-3-isoquinoline-3-carboxylic acid (4.98 g, 95.0%) as crystals.

Melting point 141-142°C.

Elemental analysis for C₁₉H₂₄NO₄F

Calculated: C, 65.31; H, 6.92; N, 4.01.

Found: C, 65.38; H, 6.86; N, 3.90.

¹H-NMR(CDCl₃) δ: 0.95 (9H, s), 0.99 (3H, t, J=7.2 Hz), 1.48-1.60 (2H, m), 1.76-1.87 (2H, m), 4.02 (2H, t, J=6.5 Hz), 4.23 (2H, bs), 7.23-7.38 (2H, m), 8.43 (1H, dd, J=5.5, 9.1 Hz).

(4) A solution (8.68 g, 45 mmol) of 4-butoxy-2-neopentyl-6-fluoro-1-oxo-1,2-dihydro-3-isoquinoline-3-carboxylic acid (1.05 g, 3 mmol) and 20% sodium methoxide in methanol was refluxed under heating for 6 h. The reaction mixture was poured into water, and, after making the mixture acidic with 1N hydrochloric acid, extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from tetrahydrofuran - diethyl ether to give 4-butoxy-6-methoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinoline-3-carboxylic acid (0.96 g, 88.9%) as crystals.

Melting point 194-196°C.

Elemental analysis for C₂₀H₂₇NO₅

Calculated: C, 66.46; H, 7.53; N, 3.88.

Found: C, 66.39; H, 7.45; N, 3.88.

¹H-NMR(CDCl₃) δ: 0.91 (9H, s), 1.01 (3H, t, J=7.2 Hz), 1.51-1.62 (2H, m), 1.76-1.87 (2H, m), 3.91 (3H, s), 4.01 (2H, t, J=6.4 Hz), 4.13 (2H, bs), 6.91 (1H, d, J=2.4 Hz), 7.08 (1H, dd, J=2.4, 8.8 Hz), 8.17 (1H, d, J=8.8 Hz).

(5) 4-Butoxy-3-hydroxymethyl-6-methoxy-2-neopentyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))

Melting point 124-125°C.

10 Elemental analysis for C₂₀H₂₉NO₄

Calculated: C, 69.14; H, 8.41; N, 4.03.

Found: C, 69.06; H, 8.41; N, 3.96.

¹H-NMR(CDCl₃) δ: 0.94 (9H, s), 1.04 (3H, t, J=7.3 Hz), 1.56-1.67 (2H, m), 1.79-1.93 (2H, m), 3.01 (1H, bs), 3.89 (2H, t, J=6.2 Hz), 3.90 (3H, s), 4.17 (2H, bs), 4.85 (2H, bs), 6.94-6.98 (2H, m), 8.15-8.21 (1H, m).

(6) 4-Butoxy-3-chloromethyl-6-methoxy-2-neopentyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

20 ¹H-NMR(CDCl₃) δ: 0.98 (9H, s), 1.04 (3H, t, J=7.4 Hz), 1.53-1.71 (2H, m), 1.82-1.95 (2H, m), 3.93 (3H, s), 3.96 (2H, t, J=6.2 Hz), 4.24 (2H, bs), 4.88 (2H, bs), 7.07-7.30 (2H, m), 8.33-8.38 (1H, m).

(7) 2-[(4-Butoxy-6-methoxy-2-neopentyl-1-oxo-1,2-

25 dihydro-3-isoquinolinyl)methyl]-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

Melting point 145-146°C.

Elemental analysis for C₂₈H₃₂N₂O₅

30 Calculated: C, 70.57; H, 6.77; N, 5.88.

Found: C, 70.60; H, 6.83; N, 5.93.

¹H-NMR(CDCl₃) δ: 1.00 (9H, s), 1.01 (3H, t, J=7.3 Hz), 1.51-1.66 (2H, m), 1.82-1.96 (2H, m), 3.92 (3H, s), 4.03 (2H, t, J=6.7 Hz), 4.24 (2H, bs), 5.07 (2H, bs), 7.06

35 (1H, dd, J=2.4, 8.8 Hz), 7.11 (1H, d, J=2.4 Hz), 7.63-7.83 (4H, m), 8.32 (1H, d, J=8.8 Hz).

(8) Tert-butyl (4-butoxy-6-methoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 1 (6))

⁵ Melting point 138.5-139°C.

Elemental analysis for C₂₅H₃₈N₂O₅

Calculated: C, 67.24; H, 8.58; N, 6.27.

Found: C, 67.31; H, 8.85; N, 6.43.

¹H-NMR(CDCl₃) δ: 0.99 (9H, s), 1.04 (3H, t, J=7.4 Hz),

¹⁰ 1.45 (9H, s), 1.51-1.64 (2H, m), 1.79-1.93 (2H, m), 3.87 (2H, t, J=6.4 Hz), 3.93 (3H, s), 4.11 (2H, bs), 4.56 (2H, t, J=5.0 Hz), 4.68 (1H, bs), 7.03-7.09 (2H, m), 8.33 (1H, d, J=9.6 Hz).

(9) 3-(Aminomethyl)-4-butoxy-6-methoxy-2-neopentyl-

¹⁵ 1(2H)-1-oxo-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 172-174°C.

Elemental analysis for C₂₀H₃₁N₂O₃Cl 1/4H₂O

²⁰ Calculated: C, 62.00; H, 8.20; N, 7.23.

Found: C, 61.90; H, 8.11; N, 7.35.

¹H-NMR(DMSO-d₆) δ: 0.90 (9H, s), 1.00 (3H, t, J=7.1 Hz), 1.52-1.64 (2H, m), 1.77-1.92 (2H, m), 3.93 (3H, s), 3.94 (2H, t, J=6.4 Hz), 4.08 (2H, bs), 4.23 (2H, bs), 7.09

²⁵ (1H, d, J=2.4 Hz), 7.20 (1H, dd, J=2.4, 8.8 Hz), 8.20 (1H, d, J=8.8 Hz), 8.59 (3H, bs).

Example 58

3-(Aminomethyl)-6-benzyloxy-4-butoxy-2-neopentyl-1(2H)-isoquinolinone hydrochloride

³⁰ (1) 6-Benzyl-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinoline-3-carboxylic acid (synthesized according to the method similar to that in Example 57 (4))

Melting point 163-164°C.

Elemental analysis for C₂₆H₃₁NO₅

³⁵ Calculated: C, 71.37; H, 7.14; N, 3.20.

Found: C, 71.13; H, 7.10; N, 2.94.

- ¹H-NMR(CDCl₃) δ: 0.89 (9H, s), 0.99 (3H, t, J=7.1 Hz), 1.41-1.59 (2H, m), 1.69-1.84 (2H, m), 3.91 (2H, t, J=6.4 Hz), 4.13 (2H, bs), 5.17 (2H, s), 7.01 (1H, d, J=2.4 Hz), 7.18 (1H, dd, J=2.4, 9.0 Hz), 7.33-7.44 (5H, m), 8.22 (1H, d, J=9.0 Hz).
- ⁵ (2) 6-Benzylxy-4-butoxy-3-hydroxymethyl-2-neopentyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4)) Melting point 95-95.5°C.
- ¹⁰ Elemental analysis for C₂₆H₃₃NO₄ Calculated: C, 73.73; H, 7.85; N, 3.31. Found: C, 73.44; H, 7.77; N, 3.38. ¹H-NMR(CDCl₃) δ: 0.95 (9H, s), 1.02 (3H, t, J=7.4 Hz), 1.45-1.64 (2H, m), 1.73-1.86 (2H, m), 2.57 (1H, bs), 3.80 (2H, t, J=6.4 Hz), 4.18 (2H, bs), 4.84 (2H, bs), 5.18 (2H, s), 7.06-7.11 (2H, m), 7.31-7.47 (5H, m), 8.23 (1H, d, J=8.0 Hz).
- ¹⁵ (3) 6-Benzylxy-4-butoxy-3-chloromethyl-2-neopentyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5)) ¹H-NMR(CDCl₃) δ: 0.97 (9H, s), 1.03 (3H, t, J=7.1 Hz), 1.46-1.65 (2H, m), 1.74-1.88 (2H, m), 3.84 (2H, t, J=6.4 Hz), 4.14 (2H, bs), 4.86 (2H, bs), 5.21 (2H, s), 7.12-7.48 (7H, m), 8.36 (1H, d, J=9.2 Hz).
- ²⁰ (4) 2-{(6-Benzylxy-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl}-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6)) Elemental analysis for C₃₄H₃₆N₂O₅ 1/2H₂O
- ²⁵ Calculated: C, 72.71; H, 6.64; N, 4.99. Found: C, 72.74; H, 6.42; N, 5.26. ¹H-NMR(CDCl₃) δ: 0.99 (3H, t, J=7.3 Hz), 1.00 (9H, s), 1.39-1.58 (2H, m), 1.64-1.89 (2H, m), 3.92 (2H, t, J=6.7 Hz), 4.10 (2H, bs), 5.06 (2H, bs), 5.20 (2H, s), 7.11-7.17 (2H, m), 7.31-7.47 (5H, m), 7.70-7.90 (4H, m), 8.30-8.35 (1H, m).

(5) Tert-butyl (6-benzyloxy-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 1 (6))

⁵ Melting point 114-115°C.

Elemental analysis for C₃₁H₄₂N₂O₅

Calculated: C, 71.42; H, 8.10; N, 5.36.

Found: C, 71.34; H, 8.40; N, 5.39.

¹H-NMR(CDCl₃) δ: 0.98 (9H, s), 1.02 (3H, t, J=7.4 Hz),

¹⁰ 1.45 (9H, s), 1.46-1.59 (2H, m), 1.73-1.87 (2H, m), 3.76 (2H, t, J=6.4 Hz), 4.11 (2H, bs), 4.54 (2H, d, J=5.2 Hz), 4.66 (1H, bs), 5.21 (2H, s), 7.08 (1H, d, J=2.6 Hz), 7.14 (1H, dd, J=2.6, 8.8 Hz), 7.32-7.48 (5H, m), 8.33 (1H, d, J=8.8 Hz).

¹⁵ (6) 3-(Aminomethyl)-6-benzyloxy-4-butoxy-2-neopentyl-1(2H)-1-oxo-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 234-236°C.

²⁰ Elemental analysis for C₂₆H₃₅N₂O₃Cl

Calculated: C, 68.03; H, 7.69; N, 6.10.

Found: C, 67.96; H, 7.64; N, 5.93.

¹H-NMR(DMSO-d₆) δ: 0.89 (9H, s), 0.98 (3H, t, J=7.5 Hz), 1.45-1.56 (2H, m), 1.71-1.82 (2H, m), 3.84 (2H, t, J=6.2 Hz), 4.07 (2H, bs), 4.21 (2H, bs), 5.33 (2H, bs), 7.11 (1H, d, J=2.2 Hz), 7.27 (1H, dd, J=2.2, 8.8 Hz), 7.34-7.50 (5H, m), 8.19 (1H, d, J=8.8 Hz), 8.52 (3H, bs).

Example 59

3-(Aminomethyl)-4-butoxy-6-hydroxy-2-neopentyl-1(2H)-isoquinolinone hydrochloride

³⁰ (1) A suspension of tert-butyl (6-benzyloxy-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (2.61 g, 5 mmol) and 5% palladium carbon (1.5 g) in tetrahydrofuran (10 ml) and ³⁵ ethanol (10 ml) was stirred under a hydrogen atmosphere at room temperature for 2 h. After filtering off 5%

palladium carbon, the filtrate was concentrated under reduced pressure. The residue was recrystallized from ethyl acetate - n-hexane to give tert-butyl (4-butoxy-6-hydroxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)-

⁵ methylcarbamate (4.98 g, 95.0%) as crystals.

Melting point 195.5-197°C.

Elemental analysis for C₂₄H₃₆N₂O₅

Calculated: C, 66.64; H, 8.39; N, 6.48.

Found: C, 66.57; H, 8.58; N, 6.49.

¹⁰ ¹H-NMR(CDCl₃) δ: 0.96 (3H, t, J=7.4 Hz), 0.99 (9H, s), 1.45 (9H, s), 1.46-1.55 (2H, m), 1.72-1.81 (2H, m), 3.82 (2H, t, J=6.6 Hz), 4.11 (2H, bs), 4.56 (2H, d, J=5.2 Hz), 4.78 (1H, bs), 7.06-7.11 (2H, m), 8.26 (1H, d, J=9.2 Hz), 8.79 (1H, bs).

¹⁵ (2) 3-(Aminomethyl)-4-butoxy-6-hydroxy-2-neopentyl-1(2H)-1-oxo-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 264-266°C.

²⁰ Elemental analysis for C₁₉H₂₉N₂O₃Cl 1/4H₂O

Calculated: C, 61.11; H, 7.96; N, 7.50.

Found: C, 61.22; H, 7.77; N, 7.56.

¹H-NMR(DMSO-d₆) δ: 0.89 (9H, s), 1.00 (3H, t, J=7.1 Hz), 1.50-1.61 (2H, m), 1.77-1.92 (2H, m), 3.89 (2H, t, J=6.2 Hz), 4.05 (2H, bs), 4.20 (2H, bs), 7.03-7.08 (2H, m), 8.11 (1H, d, J=8.2 Hz), 8.50 (1H, s), 10.67 (1H, bs).

Example 60

3-(Aminomethyl)-4-butoxy-2-neopentyl-6-propoxy-1(2H)-isoquinolinone hydrochloride

³⁰ (1) A solution of tert-butyl (4-butoxy-6-hydroxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.52 g, 1.2 mmol), 1-bromopropane (0.16 ml, 1.2 mmol) and potassium carbonate (0.16 g, 1.2 mmol) in N,N-dimethylformamide (10 ml) was ³⁵ stirred at room temperature for 12 h. The reaction mixture was poured into water and extracted with ethyl

acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl (4-butoxy-

5 2-neopentyl-1-oxo-6-propoxy-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.50 g, 89.3%) as an amorphous.

Elemental analysis for $C_{27}H_{42}N_2O_5$ 1/4H₂O

Calculated: C, 67.68; H, 8.94; N, 5.85.

10 Found: C, 67.87; H, 8.89; N, 5.95.

¹H-NMR(CDCl₃) δ: 0.99 (9H, s), 1.04 (3H, t, J=7.2 Hz), 1.08 (3H, t, J=7.4 Hz), 1.45 (9H, s), 1.50-1.65 (2H, m), 1.79-1.93 (4H, m), 3.83 (2H, t, J=6.6 Hz), 4.01 (2H, bs), 4.04 (2H, t, J=6.4 Hz), 4.55 (2H, d, J=5.2 Hz), 4.67 (1H,

15 bs), 7.02-7.08 (2H, m); 8.31 (1H, d, J=9.6 Hz).

(2) 3-(Aminomethyl)-4-butoxy-2-neopentyl-6-propoxy-1(2H)-1-oxo-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7))

20 Melting point 202-204°C.

Elemental analysis for $C_{22}H_{35}N_2O_3Cl$

Calculated: C, 64.29; H, 8.58; N, 6.82.

Found: C, 64.05; H, 8.29; N, 6.64.

¹H-NMR(DMSO-d₆) δ: 0.90 (9H, s), 1.00 (3H, t, J=7.4 Hz),

25 1.02 (3H, t, J=7.3 Hz), 1.53-1.63 (2H, m), 1.72-1.86 (4H, m), 3.94 (2H, t, J=6.2 Hz), 4.07 (2H, bs), 4.10 (2H, t, J=6.5 Hz), 4.23 (2H, bs), 7.07 (1H, d, J=2.5Hz), 7.19 (1H, dd, J=2.5, 8.8 Hz), 8.18 (1H, d, J=8.8 Hz), 8.51 (3H, bs).

30 Example 61

3-(Aminomethyl)-4,6-dibutoxy-2-neopentyl-1(2H)-isoquinolinone hydrochloride

(1) Tert-butyl (4,6-dibutoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized

35 according to the method similar to that in Example 60 (1))

Elemental analysis for C₂₈H₄₄N₂O₅

Calculated: C, 68.82; H, 9.08; N, 5.73.

Found: C, 68.66; H, 8.87; N, 5.54.

- ¹H-NMR(CDCl₃) δ: 0.99 (9H, s), 1.00 (3H, t, J=7.4 Hz),
⁵ 1.04 (3H, t, J=7.0 Hz), 1.45 (9H, s), 1.51-1.64 (4H, m),
1.77-1.90 (4H, m), 3.86 (2H, t, J=6.4 Hz), 4.08 (2H, t,
J=6.5 Hz), 4.14 (2H, bs), 4.56 (2H, d, J=5.2 Hz), 4.67
(1H, bs), 7.02-7.08 (2H, m), 8.32 (1H, d, J=9.4 Hz).
(2) 3-(Aminomethyl)-4,6-dibutoxy-2-neopentyl-1(2H)-1-
¹⁰ oxo-isoquinolinone hydrochloride (synthesized according
to the method similar to that in Example 1 (7))
Melting point 184-186°C.

Elemental analysis for C₂₃H₃₇N₂O₃Cl 3/4H₂O

Calculated: C, 63.00; H, 8.85; N, 6.39.

- ¹⁵ Found: C, 62.85; H, 8.88; N, 6.14.
¹H-NMR(DMSO-d₆) δ: 0.90 (9H, s), 0.96 (3H, t, J=7.8 Hz),
1.00 (3H, t, J=7.4 Hz), 1.42-1.60 (4H, m), 1.63-1.92 (4H,
m), 3.94 (2H, t, J=6.2 Hz), 4.11 (2H, bs), 4.15 (2H, t,
J=6.5 Hz), 4.23 (2H, bs), 7.07 (1H, d, J=2.4 Hz), 7.18
²⁰ (1H, dd, J=2.4, 8.8 Hz), 8.18 (1H, d, J=8.8 Hz), 8.57
(3H, bs).

Example 62

3-(Aminomethyl)-4-butoxy-6-(2-methoxyethoxy)-2-
neopentyl-1(2H)-isoquinolinone hydrochloride

- ²⁵ (1) Tert-butyl {4-butoxy-6-(2-methoxyethoxy)-2-
neopentyl-1-oxo-1,2-dihydro-3-
isoquinolinyl)methylcarbamate (synthesized according to
the method similar to that in Example 60 (1))

Elemental analysis for C₂₇H₄₂N₂O₆

- ³⁰ Calculated: C, 66.10; H, 8.63; N, 5.71.

Found: C, 66.22; H, 8.59; N, 5.41.

- ¹H-NMR(CDCl₃) δ: 0.99 (9H, s), 1.03 (3H, t, J=7.4 Hz),
1.45 (9H, s), 1.52-1.64 (2H, m), 1.78-1.89 (2H, m), 3.49
(3H, s), 3.80-3.88 (4H, m), 4.20 (2H, bs), 4.22-4.25 (2H,
³⁵ m), 4.55 (2H, d, J=5.4 Hz), 4.66 (1H, bs), 7.08-7.13 (2H,
m), 8.30-8.35 (1H, m).

(2) 3-(Aminomethyl)-4-butoxy-6-(2-methoxyethoxy)-2-neopentyl-1(2H)-1-oxo-isoquinolinone hydrochloride
(synthesized according to the method similar to that in Example 1 (7))

5 Melting point 188-189°C.

Elemental analysis for C₂₂H₃₅N₂O₄Cl

Calculated: C, 61.89; H, 8.26; N, 6.56.

Found: C, 61.55; H, 8.34; N, 6.59.

¹H-NMR(DMSO-d₆) δ:0.90 (9H, s), 1.00 (3H, t, J=7.3 Hz),

10 1.51-1.62 (2H, m), 1.77-1.88 (2H, m), 3.33 (3H, s), 3.71-3.75 (2H, m), 3.94 (2H, t, J=6.4 Hz), 4.07 (2H, bs), 4.25-4.30 (4H, m), 7.09 (1H, d, J=2.4Hz), 7.21 (1H, dd, J=2.4, 8.8 Hz), 8.18 (1H, d, J=8.8 Hz), 8.55 (3H, bs).

Example 63

15 3-(Aminomethyl)-7-benzyloxy-4-butoxy-2-neopentyl-1(2H)-isoquinolinone hydrochloride

(1) A solution of 5-benzyloxy-2-(ethoxycarbonyl)benzoic acid (21.86 g, 120 mmol), ethyl 2-

(neopentylamino)acetate (20.79 g, 120 mmol), 1-ethyl-3-

20 (3-dimethylaminopropyl)carbodiimide hydrochloride (28.76 g, 150 mmol) and 1-hydroxybenzotriazole (22.97 g, 150 mmol) in N,N-dimethylformamide (200 ml) was stirred at room temperature for 3 h. The reaction mixture was poured into water and extracted with ethyl acetate. The

25 extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in N,N-dimethylformamide (300 ml), and potassium carbonate (33.17 g, 240 mmol) and benzyl bromide (35.7 ml, 300 mmol) were added. The mixture was stirred at room

30 temperature for 12 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in ethanol (50 ml)

35 and 20% sodium ethoxide ethanol solution (34.04 g, 100

mmol) was added. The mixture was stirred at room temperature for 1 h. The reaction mixture was poured into 1N hydrochloric acid (150 ml) and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography and the component eluted earlier was concentrated to give ethyl 7-benzyloxy-4-hydroxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate as an oil. To a solution of the obtained ethyl 7-benzyloxy-4-hydroxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (3.26 g, 8 mmol), 1-butanol (1.1 ml, 12 mmol) and tributylphosphine (4.0 ml, 16 mmol) in tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyl)dipiperidine (4.04 g, 16 mmol) and the mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography to give ethyl 7-benzyloxy-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (3.61 g; 97.0%) as an oil.

¹H-NMR(CDCl₃) δ: 0.94 (9H, s), 1.00 (3H, t, J=7.4 Hz), 1.43 (3H, t, J=7.2 Hz), 1.51-1.66 (2H, m), 1.73-1.87 (2H, m), 3.94 (2H, t, J=6.5 Hz), 4.14 (2H, bs), 4.42 (2H, q, J=7.2 Hz), 5.20 (2H, bs), 7.34-7.50 (6H, m), 7.73 (1H, d, J=8.8 Hz), 7.96 (1H, d, J=2.6 Hz).

(2) 7-Benzyl-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinoline-3-carboxylic acid (synthesized according to the method similar to that in Example 57 (4))

Elemental analysis for C₂₆H₃₁NO₅

Calculated: C, 71.37; H, 7.14; N, 3.20.

Found: C, 71.11; H, 7.35; N, 3.08.

¹H-NMR(CDCl₃) δ: 0.91 (9H, s), 0.95 (3H, t, J=7.4 Hz), 1.44-1.59 (2H, m), 1.74-1.89 (2H, m), 4.00 (2H, t, J=6.6 Hz), 4.35 (2H, bs), 5.20 (2H, s), 7.31-7.51 (6H, m), 7.60 (1H, d, J=8.8 Hz), 7.84 (1H, d, J=2.6 Hz).

(3) 7-Benzylxy-4-butoxy-3-hydroxymethyl-2-neopentyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))
Melting point 156.5-157°C.

⁵ Elemental analysis for C₂₆H₃₃NO₄

Calculated: C, 73.73; H, 7.85; N, 3.31.

Found: C, 73.76; H, 7.62; N, 3.42.

¹H-NMR(CDCl₃) δ: 0.98 (9H, s), 1.00 (3H, t, J=7.4 Hz), 1.47-1.64 (2H, m), 1.76-1.90 (2H, m), 2.57 (1H, bs),

¹⁰ 3.87 (2H, t, J=6.4 Hz), 4.23 (2H, bs), 4.86 (2H, bs), 5.17 (2H, s), 7.25-7.51 (6H, m), 7.59 (1H, d, J=8.8 Hz), 7.82 (1H, d, J=2.2 Hz).

(4) 7-Benzylxy-4-butoxy-3-chloromethyl-2-neopentyl-1(2H)-isoquinolinone (synthesized according to the

¹⁵ method similar to that in Example 4 (5)).

¹H-NMR(CDCl₃) δ: 0.99 (9H, s), 1.03 (3H, t, J=7.4 Hz), 1.54-1.69 (2H, m), 1.80-1.94 (2H, m), 3.94 (2H, t, J=6.4 Hz), 4.17 (2H, bs), 4.90 (2H, bs), 5.20 (2H, s), 7.33-7.50 (6H, m), 7.69 (1H, d, J=8.8 Hz), 7.96 (1H, d, J=2.4

²⁰ Hz).

(5) 2-{(7-Benzylxy-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl}-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

²⁵ Melting point 120-121°C.

Elemental analysis for C₃₄H₃₆N₂O₅

Calculated: C, 73.89; H, 6.57; N, 5.07.

Found: C, 73.77; H, 6.28; N, 5.29.

¹H-NMR(CDCl₃) δ: 1.00 (3H, t, J=7.2 Hz), 1.02 (9H, s),

³⁰ 1.44-1.62 (2H, m), 1.81-1.95 (2H, m), 4.02 (2H, t, J=6.8 Hz), 4.06 (2H, bs), 5.08 (2H, bs), 5.18 (2H, s), 7.30-7.50 (6H, m), 7.67-7.90 (5H, m), 7.93 (1H, d, J=2.6 Hz).

(6) Tert-butyl (7-benzylxy-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized

³⁵ according to the method similar to that in Example 1 (6))

Melting point 122-123°C.

Elemental analysis for C₃₁H₄₂N₂O₅

Calculated: C, 71.42; H, 8.10; N, 5.36.

Found: C, 71.31; H, 8.19; N, 5.39.

5 ¹H-NMR(CDCl₃) δ:1.00 (9H, s), 1.02 (3H, t, J=7.2 Hz),
1.45 (9H, s), 1.46-1.64 (2H, m), 1.78-1.92 (2H, m), 3.86
(2H, t, J=6.6 Hz), 4.17 (2H, bs), 4.56 (2H, t, J=5.2 Hz),
4.65 (1H, bs), 5.19 (2H, s), 7.30-7.50 (6H, m), 7.64 (1H,
d, J=8.6 Hz), 7.93 (1H, d, J=2.6 Hz).

10 (7) 3-(Aminomethyl)-7-benzyloxy-4-butoxy-2-neopentyl-
1(2H)-1-oxo-isouquinoline hydrochloride (synthesized
according to the method similar to that in Example 1
(7))

Melting point 202-204°C.

15 Elemental analysis for C₂₆H₃₅N₂O₃Cl H₂O

Calculated: C, 65.46; H, 7.82; N, 5.87.

Found: C, 65.57; H, 7.47; N, 5.49.

1 ¹H-NMR(DMSO-d₆) δ:0.91 (9H, s), 0.99 (3H, t, J=7.3 Hz),
1.48-1.60 (2H, m), 1.76-1.91 (2H, m), 3.92 (2H, t, J=6.4
Hz), 4.08 (2H, bs), 4.23 (2H, bs), 5.27 (2H, s), 7.31-
7.55 (6H, m); 7.74 (1H, d, J=8.6 Hz), 7.80 (1H, d, J=2.6
Hz); 8.51 (3H, bs).

Example 64

3-(Aminomethyl)-4-butoxy-7-hydroxy-2-neopentyl-1(2H)-
25 isoquinolinone hydrochloride

(1) Tert-butyl (4-butoxy-7-hydroxy-2-neopentyl-1-oxo-
1,2-dihydro-3-isouquinolinyl)methylcarbamate (synthesized
according to the method similar to that in Example 59
(1))

30 Melting point 237-238°C.

Elemental analysis for C₂₄H₃₆N₂O₅

Calculated: C, 66.64; H, 8.39; N, 6.48.

Found: C, 66.54; H, 8.41; N, 6.36.

1 ¹H-NMR(CDCl₃) δ:0.88 (9H, s), 0.96 (3H, t, J=7.2 Hz),
1.40 (2H, m), 1.44-1.59 (9H, s), 1.40-1.55 (2H, m),
1.69-1.79 (2H, m), 3.80 (2H, t, J=6.2 Hz), 3.94 (2H, bs),

4.39 (2H, d, J=4.8 Hz), 7.21 (1H, bs), 7.24 (1H, dd, J=2.4, 8.4 Hz), 7.56 (1H, d, J=2.4 Hz), 7.58 (1H, d, J=8.4 Hz), 10.15 (1H, s).

(2) 3-(Aminomethyl)-4-butoxy-7-hydroxy-2-neopentyl-

⁵ 1(2H)-1-oxo-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 238-239°C.

Elemental analysis for C₁₉H₂₉N₂O₃Cl

¹⁰ Calculated: C, 61.86; H, 7.92; N, 7.59.

Found: C, 61.80; H, 7.84; N, 7.52.

¹H-NMR(DMSO-d₆) δ: 0.89 (9H, s), 0.98 (3H, t, J=7.3 Hz), 1.44-1.63 (2H, m), 1.75-1.89 (2H, m), 3.91 (2H, t, J=6.5 Hz), 4.08 (2H, bs), 4.20 (2H, bs), 7.31 (1H, dd, J=2.8, 8.6 Hz), 7.62 (1H, d, J=2.8 Hz), 7.64 (1H, d, J=8.6 Hz), 8.43 (3H, bs), 10.33 (1H, s).

Example 65

3-(Aminomethyl)-4-butoxy-7-methoxy-2-neopentyl-1(2H)-isoquinolinone hydrochloride

²⁰ (1) Tert-butyl (4-butoxy-7-methoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 60 (1))

Melting point 171-172°C.

²⁵ Elemental analysis for C₂₅H₃₈N₂O₅ 1/4H₂O

Calculated: C, 66.57; H, 8.60; N, 6.21.

Found: C, 66.65; H, 8.77; N, 6.15.

¹H-NMR(CDCl₃) δ: 1.00 (9H, s), 1.02 (3H, t, J=7.4 Hz), 1.45 (9H, s), 1.51-1.66 (2H, m), 1.78-1.92 (2H, m), 3.86 (2H, t, J=6.4 Hz), 3.93 (3H, s), 4.14 (2H, bs), 4.56 (2H, d, J=4.8 Hz), 4.66 (1H, bs), 7.28 (1H, dd, J=2.6, 8.8 Hz), 7.63 (1H, d, J=8.8 Hz), 7.82 (1H, d, J=2.6 Hz).

(2) 3-(Aminomethyl)-4-butoxy-7-methoxy-2-neopentyl-1(2H)-1-oxo-isoquinolinone hydrochloride (synthesized

³⁵ according to the method similar to that in Example 1 (7))

Melting point 210-212°C.

Elemental analysis for C₂₀H₃₁N₂O₃Cl

Calculated: C, 62.00; H, 8.20; N, 7.23.

Found: C, 61.97; H, 8.07; N, 7.28.

⁵ ¹H-NMR(DMSO-d₆) δ:0.91 (9H, s), 0.99 (3H, t, J=7.3 Hz), 1.45-1.64 (2H, m), 1.77-1.91 (2H, m), 3.90 (3H, s), 3.92 (2H, t, J=6.2 Hz), 4.10 (2H, bs), 4.23 (2H, bs), 7.45 (1H, dd, J=2.6, 8.8 Hz), 7.70 (1H, d, J=2.6 Hz), 7.73 (1H, d, J=8.8 Hz), 8.52 (3H, bs).

¹⁰ Example 66

3-(Aminomethyl)-4-butoxy-7-ethoxy-2-neopentyl-1(2H)-isoquinolinone hydrochloride

(1) Tert-butyl (4-butoxy-7-ethoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized

¹⁵ according to the method similar to that in Example 60

(1))

Melting point 140-142°C.

Elemental analysis for C₂₆H₄₀N₂O₅

Calculated: C, 67.80; H, 8.75; N, 6.08.

²⁰ Found: C, 67.57; H, 8.51; N, 6.10.

¹H-NMR(CDCl₃) δ:1.00 (9H, s), 1.02 (3H, t, J=7.4 Hz), 1.44 (9H, s), 1.45 (3H, t, J=7.0 Hz), 1.49-1.67 (2H, m), 1.78-1.92 (2H, m), 3.85 (2H, t, J=6.6 Hz), 4.11 (2H, bs), 4.16 (2H, q, J=7.0 Hz), 4.56 (2H, d, J=5.2 Hz), 4.65 (1H, bs), 7.27 (1H, dd, J=2.4, 8.8 Hz), 7.62 (1H, d, J=8.8 Hz), 7.80 (1H, d, J=2.4 Hz).

(2) 3-(Aminomethyl)-4-butoxy-7-ethoxy-2-neopentyl-1(2H)-1-oxo-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1

³⁰ (7))

Elemental analysis for C₂₁H₃₃N₂O₃Cl 1/2H₂O

Calculated: C, 62.13; H, 8.44; N, 6.90.

Found: C, 62.21; H, 8.40; N, 7.15.

¹H-NMR(DMSO-d₆) δ:0.91 (9H, s), 0.99 (3H, t, J=7.3 Hz),

³⁵ 1.38 (3H, t, J=6.8 Hz), 1.49-1.60 (2H, m), 1.69-1.92 (2H, m), 3.92 (2H, bs), 4.12-4.22 (6H, m), 7.44 (1H, dd,

$J=2.6, 8.8$ Hz), 7.62-7.75 (2H, m), 8.54 (3H, bs).

Example 67

3-(Aminomethyl)-4-butoxy-2-neopentyl-7-propoxy-1(2H)-isoquinolinone hydrochloride

- ⁵ (1) Tert-butyl (4-butoxy-2-neopentyl-1-oxo-7-propoxy-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 60 (1))

Melting point 143.5-144.5°C.

- ¹⁰ Elemental analysis for $C_{27}H_{42}N_2O_5$

Calculated: C, 68.32; H, 8.92; N, 5.90.

Found: C, 68.30; H, 8.95; N, 6.02.

1H -NMR(CDCl₃) δ : 1.00 (9H, s), 1.02 (3H, t, $J=7.4$ Hz), 1.06 (3H, t, $J=7.4$ Hz), 1.45 (9H, s), 1.51-1.65 (2H, m),

- ¹⁵ 1.76-1.92 (4H, m), 3.85 (2H, t, $J=6.6$ Hz), 4.06 (2H, t, $J=6.8$ Hz), 4.09 (2H, bs), 4.56 (2H, d, $J=4.4$ Hz), 4.62 (1H, bs), 7.28 (1H, dd, $J=2.7, 8.8$ Hz), 7.62 (1H, d, $J=8.8$ Hz), 7.80 (1H, d, $J=2.7$ Hz).

(2) 3-(Aminomethyl)-4-butoxy-2-neopentyl-7-propoxy-

- ²⁰ 1(2H)-1-oxo-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 216-218°C.

Elemental analysis for $C_{22}H_{35}N_2O_3Cl$ 1/4H₂O

- ²⁵ Calculated: C, 63.60; H, 8.61; N, 6.74.

Found: C, 63.84; H, 8.67; N, 6.80.

1H -NMR(DMSO-d₆) δ : 0.90 (9H, s), 0.99 (3H, t, $J=7.4$ Hz), 1.01 (3H, t, $J=7.3$ Hz), 1.49-1.70 (2H, m), 1.73-1.90 (4H, m), 3.92 (2H, t, $J=6.6$ Hz), 4.07 (2H, t, $J=6.4$ Hz), 4.10

- ³⁰ (2H, bs), 4.23 (2H, bs), 7.45 (1H, dd, $J=2.8, 8.8$ Hz), 7.68 (1H, d, $J=2.8$ Hz), 7.72 (1H, d, $J=8.8$ Hz), 8.51 (3H, bs).

Example 68

3-(Aminomethyl)-4,7-dibutoxy-2-neopentyl-1(2H)-

- ³⁵ isoquinolinone hydrochloride

(1) Tert-butyl (4-butoxy-7-butoxy-2-neopentyl-1-oxo-1,2-

dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 60 (1))

Elemental analysis for C₂₈H₄₄N₂O₅

Calculated: C, 68.82; H, 9.08; N, 5.73.

Found: C, 68.79; H, 9.34; N, 5.72.

¹H-NMR(CDCl₃) δ: 0.99 (3H, t, J=7.2 Hz), 1.00 (9H, s), 1.02 (3H, t, J=7.2 Hz), 1.45 (9H, s), 1.46-1.64 (4H, m), 1.74-1.89 (4H, m), 3.85 (2H, t, J=6.4 Hz), 4.07 (2H, bs), 4.10 (2H, t, J=6.4 Hz), 4.55 (2H, d, J=4.4 Hz), 4.61 (1H, bs), 7.28 (1H, dd, J=2.8, 8.8 Hz), 7.62 (1H, d, J=8.8 Hz), 7.80 (1H, d, J=2.8 Hz).

(2) 3-(Aminomethyl)-4,7-dibutoxy-2-neopentyl-1(2H)-1-oxo-isoquinolinone hydrochloride (synthesized according

to the method similar to that in Example 1 (7))

Melting point 192.5-193°C.

Elemental analysis for C₂₃H₃₇N₂O₃Cl 1/4H₂O

Calculated: C, 64.32; H, 8.80; N, 6.52.

Found: C, 64.38; H, 8.83; N, 6.49.

¹H-NMR(DMSO-d₆) δ: 0.91 (9H, s), 0.95-1.02 (6H, m), 1.41-1.60 (4H, m), 1.68-1.87 (4H, m), 3.92 (2H, t, J=6.1 Hz), 4.11 (2H, t, J=6.2 Hz), 4.14 (2H, bs), 4.23 (2H, bs), 7.44 (1H, dd, J=2.6, 8.8 Hz), 7.68 (1H, d, J=2.6 Hz), 7.72 (1H, d, J=8.8 Hz), 8.54 (3H, bs).

Example 69

3-(Aminomethyl)-4-butoxy-5,6-dimethoxy-2-neopentyl-1(2H)-isoquinolinone hydrochloride

(1) A solution of ethyl 6-formyl-2,3-dimethoxybenzoate (5.24 g, 22 mmol), sodium dihydrogen phosphate (3.60 g,

30 mmol) and 2-methyl-2-butene (10.3 ml, 96.8 mmol) in t-butanol (20 ml), tetrahydrofuran (20 ml) and water (20 ml) was stirred at room temperature for 10 min. To the obtained mixture was added sodium chlorite (6.76 g, 74.8 mmol) and the mixture was stirred at room temperature

for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed

- with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate - n-hexane to give 2-(ethoxycarbonyl)-3,4-dimethoxybenzoic acid (4.51 g, 80.7%) as crystals.
- Melting point 148-149°C.
- Elemental analysis for C₁₂H₁₄O₆
- Calculated: C, 56.69; H, 5.55.
- Found: C, 56.52; H, 5.64.
- 10 ¹H-NMR(CDCl₃) δ: 1.38 (3H, t, J=7.2 Hz), 3.87 (3H, s), 3.95 (3H, s), 4.43 (2H, q, J=7.2 Hz), 6.97 (1H, d, J=8.8 Hz), 7.88 (1H, d, J=8.8 Hz).
- (2) A solution of 2-(ethoxycarbonyl)-3,4-dimethoxybenzoic acid (4.45 g, 17.5 mmol), ethyl 2-(neopentylamino)acetate (3.47 g, 20 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (3.83 g, 20 mmol) in N,N-dimethylformamide (50 ml) was stirred at room temperature for 3 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in ethanol (50 ml) and 20% sodium ethoxide ethanol solution (34.04 g, 100 mmol) was added thereto. The mixture was stirred at room temperature for 1 h. The reaction mixture was poured into 1N hydrochloric acid (150 ml) and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give ethyl 5,6-dimethoxy-4-hydroxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (3.21 g, 50.6%) as an oil.
- Elemental analysis for C₁₉H₂₅NO₆ 1/2H₂O
- Calculated: C, 61.28; H, 7.04; N, 3.76.
- 35 Found: C, 61.61; H, 6.67; N, 3.85.
- ¹H-NMR(CDCl₃) δ: 0.90 (9H, s), 1.43 (3H, t, J=7.2 Hz),

4.01 (3H, s), 4.04 (3H, s), 4.21 (2H, bs), 4.44 (2H, q, J=7.2 Hz), 7.24 (1H, d, J=9.2 Hz), 8.28 (1H, d, J=9.2 Hz), 9.56 (1H, s).

- (3) Ethyl 4-butoxy-5,6-dimethoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (2))
 Melting point 70-71°C.

Elemental analysis for $C_{23}H_{33}NO_6$

Calculated: C, 65.85; H, 7.93; N, 3.34.

Found: C, 65.64; H, 7.79; N, 3.45.

1H -NMR(CDCl₃) δ: 0.95 (9H, s), 0.96 (3H, t, J=7.2 Hz), 1.34-1.52 (5H, m), 1.65-1.80 (2H, m), 3.63 (3H, s), 3.89-3.96 (4H, m), 4.00 (3H, s), 4.42 (2H, q, J=7.2 Hz), 7.19 (1H, d, J=8.8 Hz), 8.28 (1H, d, J=8.8 Hz).

- (4) 4-Butoxy-5,6-dimethoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4)

(3)
 Melting point 144-145.5°C.

- Elemental analysis for $C_{21}H_{29}NO_6 \frac{1}{4}H_2O$

Calculated: C, 63.70; H, 7.51; N, 3.54.

Found: C, 63.81; H, 7.28; N, 3.60.

1H -NMR(CDCl₃) δ: 0.91 (9H, s), 0.95 (3H, t, J=7.2 Hz), 1.37-1.52 (2H, m), 1.72-1.86 (2H, m), 3.87 (3H, s),

- 3.89-3.97 (2H, m), 4.00 (3H, s), 4.10 (2H, bs), 7.22 (1H, d, J=8.9 Hz), 8.27 (1H, d, J=8.9 Hz).

(5) 4-Butoxy-5,6-dimethoxy-3-hydroxymethyl-2-neopentyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))

- Melting point 140-141°C.

Elemental analysis for $C_{21}H_{31}NO_5 \frac{1}{4}H_2O$

Calculated: C, 66.03; H, 8.31; N, 3.67.

Found: C, 66.13; H, 8.22; N, 3.77.

1H -NMR(CDCl₃) δ: 0.97 (9H, s), 1.00 (3H, t, J=7.2 Hz),

- 1.46-1.64 (2H, m), 1.75-1.80 (2H, m), 2.39 (1H, s), 3.84 (3H, s), 3.86 (2H, t, J=7.0 Hz), 3.98 (3H, s), 4.17 (2H,

bs), 4.86 (2H, bs), 7.11 (1H, d, J=9.0 Hz), 8.20 (1H, d, J=9.0 Hz).

(6) 4-Butoxy-3-chloromethyl-5,6-dimethoxy-2-neopentyl-1(2H)-isoquinolinone (synthesized according to the

5 method similar to that in Example 4 (5))

$^1\text{H-NMR}(\text{CDCl}_3)$ δ : 0.98 (9H, s), 1.02 (3H, t, J=7.4 Hz), 1.47-1.64 (2H, m), 1.76-1.87 (2H, m), 3.85 (3H, s), 3.89 (2H, t, J=6.2 Hz), 3.99 (3H, s), 4.12 (2H, bs), 4.92 (2H, bs), 7.24 (1H, d, J=8.8 Hz), 8.28 (1H, d, J=8.8 Hz).

10 (7) 2-{{(4-Butoxy-5,6-dimethoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl}-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

Melting point 122-123°C.

15 Elemental analysis for $\text{C}_{29}\text{H}_{34}\text{N}_2\text{O}_6$

Calculated: C, 68.76; H, 6.76; N, 5.53.

Found: C, 68.72; H, 6.71; N, 5.58.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ : 0.95 (3H, t, J=7.4 Hz), 0.99 (9H, s), 1.41-1.53 (2H, m), 1.75-1.89 (2H, m), 3.86 (3H, s),

20 3.94-3.95 (4H, m), 3.99 (3H, s), 5.13 (2H, bs), 7.15 (1H, d, J=9.0 Hz), 7.67-7.84 (4H, m), 8.25 (1H, d, J=9.0 Hz); (8) Tert-butyl (4-butoxy-5,6-dimethoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate

(synthesized according to the method similar to that in

25 Example 1 (6))

Elemental analysis for $\text{C}_{26}\text{H}_{40}\text{N}_2\text{O}_6$

Calculated: C, 65.52; H, 8.46; N, 5.88.

Found: C, 65.17; H, 8.30; N, 5.89.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ : 0.98 (9H, s), 0.99 (3H, t, J=7.3 Hz),

30 1.45 (9H, s), 1.46-1.55 (2H, m), 1.74-1.84 (2H, m), 3.80 (2H, t, J=6.2 Hz), 3.85 (3H, s), 3.99 (3H, s), 4.14 (2H, bs), 4.56 (2H, d, J=5.6 Hz), 4.67 (1H, bs), 7.15 (1H, d, J=9.0 Hz), 8.26 (1H, d, J=9.0 Hz).

(9) 3-(Aminomethyl)-4-butoxy-5,6-dimethoxy-2-neopentyl-

35 1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1

(7))

Melting point 156-157°C.

Elemental analysis for C₂₁H₃₃N₂O₄Cl

Calculated: C, 61.08; H, 8.05; N, 6.78.

5 Found: C, 60.71; H, 8.05; N, 6.78.

¹H-NMR(DMSO-d₆) δ:0.88 (9H, s), 0.97 (3H, t, J=7.3 Hz), 1.43-1.54 (2H, m), 1.76-1.83 (2H, m), 3.76 (3H, s), 3.79 (2H, bs), 3.94 (3H, s), 4.07 (2H, bs), 4.22 (2H, s), 7.40 (1H, d, J=9.0 Hz), 8.11 (1H, d, J=9.0 Hz), 8.52 (3H,

10 bs).

Example 70

3-(Aminomethyl)-4-butoxy-6,7-dimethoxy-2-neopentyl-1(2H)-isoquinolinone hydrochloride

(1) 2-(Ethoxycarbonyl)-4,5-dimethoxybenzoic acid

15 synthesized according to the method similar to that in

Example 69 (1))

Melting point 130-131°C.

Elemental analysis for C₁₂H₁₄O₆ 1/4H₂O

Calculated: C, 55.70; H, 5.65.

20 Found: C, 56.06; H, 5.53.

¹H-NMR(CDCl₃) δ:1.39 (3H, t, J=7.2 Hz), 3.98 (6H, s), 4.40 (2H, q, J=7.2 Hz), 7.22 (1H, s), 7.50 (1H, s), 8.01 (1H, s).

(2) Ethyl 6,7-dimethoxy-4-hydroxy-2-neopentyl-1-oxo-1,2-dihydro-3-isooquinolinecarboxylate (synthesized according to the method similar to that in Example 69 (2))

Elemental analysis for C₁₉H₂₅NO₆

Calculated: C, 62.80; H, 6.93; N, 3.85.

Found: C, 62.58; H, 6.89; N, 3.82.

30 ¹H-NMR(CDCl₃) δ:0.85 (9H, s), 1.47 (3H, t, J=7.2 Hz), 4.04 (6H, s), 4.47 (2H, q, J=7.2 Hz), 4.55 (2H, bs), 7.49 (1H, s), 7.85 (1H, s), 11.04 (1H, s).

(3) Ethyl 4-butoxy-6,7-dimethoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isooquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (2))

¹H-NMR(CDCl₃) δ:0.94 (9H, s), 1.02 (3H, t, J=7.3 Hz),

- 1.44 (3H, t, J=7.3 Hz), 1.49-1.67 (2H, m), 1.74-1.87 (2H, m), 3.96 (2H, t, J=6.4 Hz), 4.01 (3H, s), 4.02 (3H, s), 4.14 (2H, bs), 4.42 (2H, q, J=7.1 Hz), 7.15 (1H, s), 7.83 (1H, s).
- ⁵ (4) 4-Butoxy-6,7-dimethoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))
Melting point 209-210°C.
- ¹⁰ Elemental analysis for C₂₁H₂₉NO₆
Calculated: C, 64.43; H, 7.47; N, 3.58.
Found: C, 64.14; H, 7.34; N, 3.46.
¹H-NMR(CDCl₃) δ: 0.91 (9H, s), 1.01 (3H, t, J=7.2 Hz), 1.44-1.65 (2H, m), 1.74-1.88 (2H, m), 3.92 (3H, s), 4.03-4.18 (7H, m); 6.60 (1H, s), 7.31 (1H, s).
- ¹⁵ (5) 4-Butoxy-6,7-dimethoxy-3-hydroxymethyl-2-neopentyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))
Melting point 142-143°C.
- ²⁰ Elemental analysis for C₂₁H₃₁NO₅ 1/4H₂O
Calculated: C, 66.03; H, 8.31; N, 3.67.
Found: C, 66.32; H, 8.46; N, 3.83.
¹H-NMR(CDCl₃) δ: 0.95 (9H, s), 1.03 (3H, t, J=7.3 Hz), 1.55-1.67 (2H, m), 1.77-1.87 (2H, m), 3.65 (1H, bs), 3.80 (2H, t, J=6.2 Hz), 3.95 (3H, s), 4.02 (3H, s), 4.22 (2H, bs), 4.84 (2H, bs), 6.76 (1H, s), 7.57 (1H, s).
- ²⁵ (6) 4-Butoxy-3-chloromethyl-6,7-dimethoxy-2-neopentyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))
³⁰ ¹H-NMR(CDCl₃) δ: 1.00 (9H, s), 1.05 (3H, t, J=7.3 Hz), 1.58-1.73 (2H, m), 1.82-1.93 (2H, m), 3.97 (2H, t, J=6.4 Hz), 4.02 (6H, s), 4.21 (2H, bs), 4.90 (2H, bs), 7.12 (1H, s), 7.82 (1H, s).
³⁵ (7) 2-{(4-Butoxy-6,7-dimethoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl}-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to

that in Example 4 (6))

Melting point 210-212°C.

Elemental analysis for C₂₉H₃₄N₂O₆

Calculated: C, 68.76; H, 6.76; N, 5.53.

⁵ Found: C, 68.61; H, 6.65; N, 5.55.

¹H-NMR(CDCl₃) δ:1.01 (3H, t, J=7.4 Hz), 1.02 (9H, s), 1.49-1.67 (2H, m), 1.82-1.96 (2H, m), 3.99 (3H, s), 4.00 (3H, s), 4.03 (2H, t, J=6.6 Hz), 4.10 (2H, bs), 5.07 (2H, s), 7.13 (1H, s), 7.68-7.83 (5H, m).

¹⁰ (8) Tert-butyl (4-butoxy-6,7-dimethoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate
(synthesized according to the method similar to that in Example 1 (6))

Melting point 197-198°C.

¹⁵ Elemental analysis for C₂₆H₄₀N₂O₆ 1/2H₂O

Calculated: C, 64.31; H, 8.51; N, 5.77.

Found: C, 64.68; H, 8.43; N, 5.62.

¹H-NMR(CDCl₃) δ:1.00 (9H, s), 1.04 (3H, t, J=7.2 Hz), 1.46 (9H, s), 1.55-1.70 (2H, m), 1.79-1.93 (2H, m), 3.86 (2H, t, J=6.4 Hz), 4.00 (3H, s), 4.05 (3H, s), 4.10 (2H, bs), 4.56 (2H, d, J=5.4 Hz), 4.80 (1H, bs), 7.03 (1H, s), 7.77 (1H, s).

(9) 3-(Aminomethyl)-4-butoxy-6,7-dimethoxy-2-neopentyl-1(2H)-isoquinolinone hydrochloride (synthesized

²⁵ according to the method similar to that in Example 1 (7))

Melting point 231-233°C.

Elemental analysis for C₂₁H₃₃N₂O₄Cl H₂O

Calculated: C, 58.53; H, 8.19; N, 6.50.

³⁰ Found: C, 58.77; H, 8.23; N, 6.61.

¹H-NMR(DMSO-d₆) δ:0.90 (9H, s), 1.00 (3H, t, J=7.3 Hz), 1.53-1.65 (2H, m), 1.77-1.88 (2H, m), 3.90 (3H, s), 3.94 (3H, s), 3.95 (2H, t, J=7.8 Hz), 4.09 (2H, bs), 4.22 (2H, s), 7.10 (1H, s), 7.65 (1H, s), 8.56 (3H, bs).

³⁵ Example 71

5-(Aminomethyl)-4-butoxy-6-neopentylthieno[2,3-

c]pyridin-7(6H)-one hydrochloride

(1) 3-(Ethoxycarbonyl)-2-thiophenecarboxylic acid

(synthesized according to the method similar to that in Example 69 (1))

⁵ Melting point 80-81°C.Elemental analysis for C₈H₈O₄S

Calculated: C, 47.99; H, 4.03.

Found: C, 47.91; H, 3.79.

¹H-NMR(CDCl₃) δ:1.46 (3H, t, J=7.1 Hz), 4.50 (2H, q,¹⁰ J=7.1 Hz), 7.57 (1H, d, J=5.3 Hz), 7.63 (1H, d, J=5.3 Hz).

(2) Ethyl 4-hydroxy-6-neopentyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridin-5-carboxylate (synthesized according to the method similar to that in Example 69

¹⁵ (2))

Melting point 95.5-97°C.

Elemental analysis for C₁₅H₁₉NO₄S

Calculated: C, 58.23; H, 6.19; N, 4.53.

Found: C, 58.12; H, 6.01; N, 4.48.

²⁰ ¹H-NMR(CDCl₃) δ:0.85 (9H, s), 1.46 (3H, t, J=7.2 Hz), 4.47 (2H, q, J=7.2 Hz), 4.53 (2H, bs), 7.55 (1H, d, J=5.1 Hz), 7.72 (1H, d, J=5.1 Hz), 10.66 (1H, s).

(3) Ethyl 4-butoxy-6-neopentyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-5-carboxylate (synthesized

²⁵ according to the method similar to that in Example 1 (2))

Melting point 74-74.5°C.

Elemental analysis for C₁₉H₂₇NO₄S

Calculated: C, 62.44; H, 7.45; N, 3.83.

³⁰ Found: C, 62.48; H, 7.70; N, 3.89.¹H-NMR(CDCl₃) δ:0.94 (9H, s), 0.99 (3H, t, J=7.3 Hz), 1.43 (3H, t, J=7.2 Hz), 1.49-1.60 (2H, m), 1.70-1.84 (2H, m), 4.00 (2H, t, J=6.6 Hz), 4.14 (2H, bs), 4.41 (2H, q, J=7.2 Hz), 7.32 (1H, d, J=5.2 Hz), 7.72 (1H, d, J=5.2 Hz).³⁵ (4) 4-Butoxy-6-neopentyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-5-carboxylic acid (synthesized according to

the method similar to that in Example 4 (3))

Melting point 111-112°C.

Elemental analysis for C₁₇H₂₃NO₄S

Calculated: C, 60.51; H, 6.87; N, 4.15.

⁵ Found: C, 60.53; H, 6.87; N, 4.29.

¹H-NMR(CDCl₃) δ:0.95 (9H, s), 0.98 (3H, t, J=7.4 Hz), 1.43-1.61 (2H, m), 1.74-1.84 (2H, m), 4.08 (2H, t, J=6.4 Hz), 4.31 (2H, bs), 5.98 (1H, bs), 7.34 (1H, d, J=5.2 Hz), 7.75 (1H, d, J=5.2Hz).

¹⁰ (5) 4-Butoxy-5-hydroxymethyl-6-neopentylthieno[2,3-c]pyridin-7(6H)-one (synthesized according to the method similar to that in Example 4 (4))

Melting point 110-111°C.

Elemental analysis for C₁₇H₂₅NO₃S

¹⁵ Calculated: C, 63.13; H, 7.79; N, 4.33.

Found: C, 63.11; H, 7.59; N, 4.44.

¹H-NMR(CDCl₃) δ:0.97 (9H, s), 1.02 (3H, t, J=7.4 Hz), 1.47-1.68 (2H, m), 1.76-1.89 (2H, m), 3.98 (2H, t, J=6.6 Hz), 4.22 (2H, bs), 4.86 (2H, bs), 7.24 (1H, d, J=5.4 Hz), 7.62 (1H, d, J=5.4 Hz).

²⁰ (6) 4-Butoxy-5-chloromethyl-6-neopentylthieno[2,3-c]pyridin-7(6H)-one (synthesized according to the method similar to that in Example 4 (5))

¹H-NMR(CDCl₃) δ:1.01 (9H, s), 1.02 (3H, t, J=7.3 Hz),

²⁵ 1.52-1.63 (2H, m), 1.78-1.88 (2H, m), 4.01 (2H, t, J=6.4 Hz), 4.20 (2H, bs), 4.89 (2H, bs), 7.30 (1H, d, J=5.2 Hz), 7.69 (1H, d, J=5.2 Hz).

(7) 2-((4-Butoxy-6-neopentyl-7-oxo-6,7-dihydrothieno{2,3-c}pyridin-5-yl)methyl)-1H-isoindole-

³⁰ 1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

Melting point 118-119°C.

Elemental analysis for C₂₅H₂₈N₂O₄S

Calculated: C, 66.35; H, 6.24; N, 6.19.

³⁵ Found: C, 66.26; H, 6.17; N, 6.27.

¹H-NMR(CDCl₃) δ:0.99 (3H, t, J=7.2 Hz), 1.03 (9H, s),

1.41-1.60 (2H, m), 1.76-1.91 (2H, m), 4.08 (2H, t, J=6.8 Hz), 4.14 (2H, bs), 5.08 (2H, s), 7.30 (1H, d, J=5.0 Hz), 7.67 (1H, d, J=5.0 Hz), 7.69-7.84 (4H, m).

- (8) Tert-butyl (4-butoxy-6-neopentyl-7-oxo-6,7-
⁵ dihydrothieno[2,3-c]pyridin-5-yl)methylcarbamate
 (synthesized according to the method similar to that in Example 1 (6))

Melting point 131-131.5°C.

Elemental analysis for C₂₂H₃₄N₂O₄S

¹⁰ Calculated: C, 62.53; H, 8.11; N, 6.63.

Found: C, 62.47; H, 8.13; N, 6.63.

¹H-NMR(CDCl₃) δ: 1.01 (9H, s), 1.02 (3H, t, J=7.1 Hz), 1.44 (9H, s), 1.46-1.68 (2H, m), 1.75-1.89 (2H, m), 3.93 (2H, t, J=6.4 Hz), 4.17 (2H, bs), 4.56 (2H, d, J=5.2 Hz),

¹⁵ 4.70 (1H, bs), 7.27 (1H, d, J=5.5 Hz), 7.68 (1H, d, J=5.5 Hz).

(9) 5-(Aminomethyl)-4-butoxy-6-neopentylthieno[2,3-c]pyridin-7(6H)-one hydrochloride (synthesized according to the method similar to that in Example 1 (7))

²⁰ Elemental analysis for C₁₇H₂₇N₂O₂ClS · 1/4H₂O

Calculated: C, 56.18; H, 7.63; N, 7.71.

Found: C, 56.01; H, 7.64; N, 7.67.

¹H-NMR(DMSO-d₆) δ: 0.91 (9H, s), 0.97 (3H, t, J=7.4 Hz), 1.45-1.56 (2H, m), 1.73-1.83 (2H, m), 4.01 (2H, t, J=6.2

²⁵ Hz), 4.13 (2H, bs), 4.23 (2H, bs), 7.47 (1H, d, J=5.1 Hz), 8.16 (1H, d, J=5.1 Hz), 8.53 (3H, bs).

Example 72

6-(Aminomethyl)-7-butoxy-5-neopentylthieno[3,2-c]pyridin-4(5H)-one hydrochloride

³⁰ (1) 2-(Ethoxycarbonyl)-3-thiophenecarboxylic acid
 (synthesized according to the method similar to that in Example 69 (1))

Melting point 94-95°C.

Elemental analysis for C₈H₈O₄S

³⁵ Calculated: C, 47.99; H, 4.03.

Found: C, 47.91; H, 3.79.

¹H-NMR(CDCl₃) δ: 1.28 (3H, t, J=7.0 Hz), 4.28 (2H, q, J=7.0 Hz), 7.32 (1H, d, J=5.1 Hz), 7.89 (1H, d, J=5.1 Hz).

- (2) Ethyl 7-hydroxy-5-neopentyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-6-carboxylate (synthesized according to the method similar to that in Example 69 (2))

Melting point 110-111°C.

Elemental analysis for C₁₅H₁₉NO₄S

Calculated: C, 58.23; H, 6.19; N, 4.53.

Found: C, 58.28; H, 6.19; N, 4.50.

¹H-NMR(CDCl₃) δ: 0.86 (9H, s), 1.47 (3H, t, J=7.2 Hz), 4.48 (2H, q, J=7.2 Hz), 7.58 (1H, d, J=5.2 Hz), 7.72 (1H, d, J=5.2 Hz), 10.62 (1H, s).

- (3) Ethyl 7-butoxy-5-neopentyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-6-carboxylate (synthesized according to the method similar to that in Example 1)

(2)

¹H-NMR(CDCl₃) δ: 0.94 (9H, s), 0.99 (3H, t, J=7.5 Hz),

1.43 (3H, t, J=7.2 Hz), 1.43-1.61 (2H, m), 1.70-1.84 (2H, m), 4.07 (2H, t, J=6.6 Hz), 4.14 (2H, bs), 4.41 (2H, q, J=7.2 Hz), 7.41 (1H, d, J=5.3 Hz), 7.68 (1H, d, J=5.3 Hz).

(4) 7-Butoxy-5-neopentyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-6-carboxylic acid (synthesized according to

- the method similar to that in Example 4 (3))

Melting point 137-138°C.

Elemental analysis for C₁₇H₂₃NO₄S

Calculated: C, 60.51; H, 6.87; N, 4.15.

Found: C, 60.66; H, 6.86; N, 4.10.

¹H-NMR(CDCl₃) δ: 0.93 (9H, s), 0.98 (3H, t, J=7.4 Hz), 1.43-1.61 (2H, m), 1.72-1.86 (2H, m), 4.14 (2H, t, J=6.4 Hz), 4.21 (2H, bs), 6.83 (1H, bs), 7.44 (1H, d, J=5.3 Hz), 7.68 (1H, d, J=5.3 Hz).

(5) 7-Butoxy-6-hydroxymethyl-5-neopentylthieno[3,2-

- c]pyridin-4(5H)-one (synthesized according to the method similar to that in Example 4 (4))

Melting point 102-103°C.

Elemental analysis for C₁₇H₂₅NO₃S 1/2H₂O

Calculated: C, 61.42; H, 7.88; N, 4.21.

Found: C, 61.39; H, 7.61; N, 4.36.

⁵ ¹H-NMR(CDCl₃) δ: 0.95 (9H, s), 1.02 (3H, t, J=7.2 Hz), 1.47-1.66 (2H, m), 1.75-1.89 (2H, m), 3.10 (1H, bs), 4.04 (2H, t, J=6.5 Hz), 4.15 (2H, bs), 4.83 (2H, bs), 7.22-7.26 (1H, m), 7.52-7.56 (1H, m).

(6) 7-Butoxy-6-chloromethyl-5-neopentylthieno[3,2-

¹⁰ c]pyridin-4(5H)-one (synthesized according to the method similar to that in Example 4 (5))

¹H-NMR(CDCl₃) δ: 1.01 (9H, s), 1.02 (3H, t, J=7.3 Hz), 1.52-1.63 (2H, m), 1.77-1.88 (2H, m), 4.08 (2H, t, J=6.4 Hz), 4.14 (2H, bs); 4.87 (2H, bs), 7.35 (1H, d, J=5.5

¹⁵ Hz), 7.68 (1H, d, J=5.5 Hz).

(7) 2-{(7-Butoxy-5-neopentyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridin-6-yl)methyl}-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

²⁰ Melting point 136-137°C.

Elemental analysis for C₂₅H₂₈N₂O₄S

Calculated: C, 66.35; H, 6.24; N, 6.19.

Found: C, 66.27; H, 6.14; N, 6.22.

¹H-NMR(CDCl₃) δ: 0.99 (3H, t, J=7.2 Hz), 1.02 (9H, s),

²⁵ 1.45-1.60 (2H, m), 1.76-1.90 (2H, m), 4.14 (2H, bs), 4.16 (2H, t, J=6.6 Hz), 5.07 (2H, s), 7.29 (1H, d, J=5.2 Hz), 7.64 (1H, d, J=5.2 Hz), 7.69-7.83 (4H, m).

(8) Tert-butyl (7-butoxy-5-neopentyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridin-6-yl)methylcarbamate

³⁰ (synthesized according to the method similar to that in Example 1 (6))

Melting point 141-142°C.

Elemental analysis for C₂₂H₃₄N₂O₄S

Calculated: C, 62.53; H, 8.11; N, 6.63.

³⁵ Found: C, 62.50; H, 8.08; N, 6.66.

¹H-NMR(CDCl₃) δ: 1.01 (9H, s), 1.02 (3H, t, J=7.1 Hz),

1.44 (9H, s), 1.49-1.64 (2H, m), 1.74-1.88 (2H, m), 4.00 (2H, t, J=6.4 Hz), 4.14 (2H, bs), 4.56 (2H, d, J=5.0 Hz), 4.70 (1H, bs), 7.29 (1H, d, J=5.1 Hz), 7.64 (1H, d, J=5.1 Hz).

⁵ (9) 6-(Aminomethyl)-7-butoxy-5-neopentylthieno[3,2-c]pyridin-4(5H)-one hydrochloride (synthesized according to the method similar to that in Example 1 (7))
Melting point 204-206°C.

Elemental analysis for C₁₇H₂₇N₂O₂ClS

¹⁰ Calculated: C, 56.89; H, 7.58; N, 7.80.
Found: C, 56.98; H, 7.46; N, 7.61.
¹H-NMR(DMSO-d₆) δ:0.91 (9H, s), 0.98 (3H, t, J=7.4 Hz), 1.44-1.59 (2H, m), 1.71-1.92 (2H, m), 4.07 (2H, t, J=6.4 Hz), 4.09 (2H, bs), 4.24 (2H, d, J=5.3 Hz), 7.56 (1H, d, J=5.3 Hz), 7.77 (1H, d, J=5.3 Hz), 8.58 (3H, bs).

Example 74

3-(Aminomethyl)-6-bromo-4-butoxy-2-isobutyl-1(2H)-isoquinolinone hydrochloride

²⁰ (1) Ethyl 6-bromo-4-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (1))
Melting point 74-75°C.

Elemental analysis for C₁₆H₁₈NO₄Br

Calculated: C, 52.19; H, 4.93; N, 3.80.

²⁵ Found: C, 52.15; H, 4.89; N, 3.85.
¹H-NMR(CDCl₃) δ:0.82 (6H, d, J=6.6 Hz), 1.46 (3H, t, J=7.2 Hz), 1.78-1.88 (1H, m), 4.39 (2H, d, J=5.6 Hz), 4.49 (2H, q, J=7.2 Hz), 7.78 (1H, dd, J=2.0, 8.4 Hz), 8.30 (1H, d, J=2.0 Hz), 8.31 (1H, d, J=8.4 Hz), 11.14 (1H, s).

³⁰ (2) Ethyl 6-bromo-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (2))
Melting point 88-89°C.

³⁵ Elemental analysis for C₂₀H₂₆NO₄Br

Calculated: C, 56.61; H, 6.18; N, 3.30.

Found: C, 56.64; H, 6.13; N, 3.38.

¹H-NMR(CDCl₃) δ:0.90 (6H, d, J=7.0 Hz), 1.01 (3H, t, J=7.4 Hz), 1.44 (3H, t, J=7.2 Hz), 1.48-1.63 (2H, m), 1.72-1.83 (2H, m), 2.05-2.19 (1H, m), 3.88 (2H, d, J=7.4 Hz), 3.95 (2H, t, J=6.4 Hz), 4.46 (2H, q, J=7.2 Hz), 7.65 (1H, dd, J=2.0, 8.6 Hz), 7.88 (1H, d, J=2.0 Hz), 8.29 (1H, d, J=8.6 Hz).

(3) 6-Bromo-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))

Melting point 177-178°C.

Elemental analysis for C₁₈H₂₂NO₄Br

Calculated: C, 54.56; H, 5.60; N, 3.53.

Found: C, 54.57; H, 5.63; N, 3.57.

(15) ¹H-NMR(CDCl₃) δ:0.90 (6H, d, J=6.6 Hz), 1.00 (3H, t, J=7.4 Hz), 1.45-1.63 (2H, m), 1.75-1.89 (2H, m), 2.07-2.23 (1H, m), 4.01 (2H, t, J=6.4 Hz), 4.02 (2H, d, J=8.6 Hz), 6.81 (1H, bs), 7.65 (1H, dd, J=1.8, 8.6 Hz), 7.81 (1H, d, J=1.8 Hz), 8.23 (1H, d, J=8.6 Hz).

(20) (4) 6-Bromo-4-butoxy-3-hydroxymethyl-2-isobutyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))

Melting point 92-93°C.

Elemental analysis for C₁₈H₂₄NO₃Br 1/2H₂O

(25) Calculated: C, 55.25; H, 6.43; N, 3.58.

Found: C, 55.62; H, 6.35; N, 3.75.

¹H-NMR(CDCl₃) δ:0.93 (6H, d, J=6.6 Hz), 1.04 (3H, t, J=7.4 Hz), 1.50-1.68 (2H, m), 1.79-1.93 (2H, m), 2.11-2.28 (1H, m), 2.47 (1H, bs), 3.88 (2H, t, J=6.4 Hz),

(30) 4.08 (2H, d, J=7.8 Hz), 4.80 (2H, s), 7.55 (1H, d, J=8.6 Hz), 7.80 (1H, s), 8.18 (1H, d, J=8.6 Hz).

(5) 6-Bromo-4-butoxy-3-chloromethyl-2-isobutyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

(35) ¹H-NMR(CDCl₃) δ:0.95 (6H, d, J=7.0 Hz), 1.05 (3H, t, J=7.2 Hz), 1.52-1.75 (2H, m), 1.86-1.96 (2H, m), 2.04-

2.23 (1H, m), 3.98 (2H, t, J=6.4 Hz), 4.07 (2H, d, J=7.4 Hz), 4.80 (2H, s), 7.63 (1H, dd, J=2.0, 8.4 Hz), 7.88 (1H, d, J=2.0 Hz), 8.29 (1H, d, J=8.4 Hz).

(6) 2-{{(6-Bromo-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl}-1H-isoindole-1,3(2H)-dione
synthesized according to the method similar to that in Example 4 (6))

¹H-NMR(CDCl₃) δ: 0.96 (6H, d, J=7.0 Hz), 1.00 (3H, t, J=7.3 Hz), 1.44-1.58 (2H, m), 1.79-1.95 (2H, m), 2.08-2.22 (1H, m), 3.95-4.05 (4H, m), 5.02 (2H, s), 7.59 (1H, dd, J=2.0, 8.8 Hz), 7.71-7.90 (5H, m), 8.27 (1H, d, J=8.8 Hz).

(7) Tert-butyl (6-bromo-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 1 (6))

Melting point 138-139°C.

Elemental analysis for C₂₃H₃₃N₂O₄Br

Calculated: C, 57.38; H, 6.91; N, 5.82.
Found: C, 57.41; H, 6.79; N, 5.76.

¹H-NMR(CDCl₃) δ: 0.95 (6H, d, J=6.6 Hz), 1.04 (3H, t, J=7.3 Hz), 1.46 (9H, s), 1.53-1.67 (2H, m), 1.80-1.93 (2H, m), 2.05-2.23 (1H, m), 3.85 (2H, t, J=6.6 Hz), 3.98 (2H, d, J=7.6 Hz), 4.41 (2H, d, J=5.4 Hz), 4.73 (1H, bs), 7.59 (1H, dd, J=2.0, 8.6 Hz), 7.82 (1H, d, J=2.0 Hz), 8.26 (1H, d, J=8.6 Hz).

(8) 3-(Aminomethyl)-6-bromo-4-butoxy-2-isobutyl-1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 133-134°C.

Elemental analysis for C₁₈H₂₆N₂O₂BrCl 1/2H₂O

Calculated: C, 50.66; H, 6.38; N, 6.56.
Found: C, 51.05; H, 6.56; N, 6.68.
¹H-NMR(DMSO-d₆) δ: 0.88 (6H, d, J=7.0 Hz), 1.00 (3H, t, J=7.4 Hz), 1.46-1.65 (2H, m), 1.76-1.91 (2H, m), 1.96-2.10 (1H, m), 3.93 (2H, t, J=6.4 Hz), 3.96 (2H, d, J=7.6

Hz), 4.18 (2H, d, J=4.4 Hz), 7.79 (1H, dd, J=2.0, 8.6 Hz), 7.87 (1H, d, J=2.0 Hz), 8.20 (1H, d, J=8.6 Hz), 8.69 (3H, bs).

Example 75

- 5 Methyl 3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylate hydrochloride
 (1). A mixture of tert-butyl (6-bromo-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to 10 the method similar to that in Example 74 (7)) (2.41 g, 5 mmol), 1,3-bis(diphenylphosphino)propane (0.21 g, 0.5 mmol) and triethylamine (0.77 ml, 5.5 mmol) in dimethyl sulfoxide (30 ml) and methanol (20 ml) was stirred under a carbon monoxide atmosphere at room temperature for 10 15 min. To the obtained mixture was added palladium acetate (0.11 g, 0.5 mmol) and the mixture was stirred with heating under a carbon monoxide atmosphere at 60°C for 12 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the 20 extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give methyl 4-butoxy-3-{{(tert-butoxycarbonyl)amino}methyl}-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylate (1.92 g, 83.5%) as 25 crystals.
- Melting point 148-149°C.
- Elemental analysis for $C_{25}H_{36}N_2O_6$
- Calculated: C, 65.20; H, 7.88; N, 6.08.
- 30 Found: C, 65.30; H, 7.67; N, 6.17.
- 1H -NMR($CDCl_3$) δ : 0.97 (6H, d, J=6.8 Hz), 1.05 (3H, t, J=7.3 Hz), 1.47 (9H, s), 1.56-1.71 (2H, m), 1.83-1.93 (2H, m), 2.05-2.25 (1H, m), 3.89 (2H, t, J=6.6 Hz), 3.99 (3H, s), 4.01 (2H, d, J=7.6 Hz), 4.53 (2H, d, J=5.4 Hz), 35 4.77 (1H, bs), 8.09 (1H, dd, J=1.9, 8.4 Hz), 8.40 (1H, d, J=1.9 Hz), 8.47 (1H, d, J=8.4 Hz).

(2) Methyl 3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylate hydrochloride
(synthesized according to the method similar to that in Example 1 (7))

5 Melting point 135-136°C.

Elemental analysis for C₂₀H₂₉N₂O₄Cl

Calculated: C, 60.52; H, 7.36; N, 7.06.

Found: C, 60.20; H, 7.48; N, 7.02.

¹H-NMR(DMSO-d₆) δ:0.89 (6H, d, J=6.6 Hz), 1.02 (3H, t,

10 J=7.3 Hz), 1.51-1.70 (2H, m), 1.80-1.92 (2H, m), 1.99-2.11 (1H, m), 3.95-4.01 (7H, m), 4.21 (2H, s), 8.11 (1H, dd, J=1.4, 8.2 Hz), 8.35 (1H, d, J=1.4 Hz), 8.41 (1H, d, J=8.2 Hz), 8.70 (3H, bs).

Example 76

15 3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid hydrochloride

(1) To a solution of methyl 4-butoxy-3-{{(tert-butoxycarbonyl)amino}methyl}-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 75 (1)) (1.61 g, 3.5 mmol) in tetrahydrofuran (10 ml) and methanol (10 ml) was added 1N sodium hydroxide (5 ml). The obtained mixture was stirred at room temperature for 2 h. The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate.

The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diethyl ether to give 4-butoxy-3-

30 {{(tert-butoxycarbonyl)amino}methyl}-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid (1.54 g, 98.7%) as crystals.

Melting point 185-186°C.

Elemental analysis for C₂₄H₃₄N₂O₆

35 Calculated: C, 64.55; H, 7.67; N, 6.27.

Found: C, 64.77; H, 7.40; N, 6.10.

- ¹H-NMR(CDCl₃) δ: 0.96 (6H, d, J=6.6 Hz), 1.07 (3H, t, J=7.4 Hz), 1.49 (9H, s), 1.50-1.72 (2H, m), 1.84-1.98 (2H, m), 2.14-2.21 (1H, m), 3.90 (2H, t, J=6.4 Hz), 4.00 (2H, d, J=6.8 Hz), 4.55 (2H, d, J=5.0 Hz), 5.37 (1H, bs), 8.08-8.13 (1H, m), 8.35-8.46 (2H, m).
- (2) 3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic hydrochloride (synthesized according to the method similar to that in Example 1 (7))
- 10 Melting point 238-239°C.
- Elemental analysis for C₁₉H₂₇N₂O₄Cl
- Calculated: C, 59.60; H, 7.11; N, 7.32.
- Found: C, 59.42; H, 7.04; N, 7.18.
- ¹H-NMR(DMSO-d₆) δ: 0.89 (6H, d, J=6.6 Hz), 1.01 (3H, t, J=7.4 Hz), 1.50-1.69 (2H, m), 1.80-1.93 (2H, m), 1.99-2.12 (1H, m), 3.97 (2H, t, J=6.4 Hz), 3.99 (2H, d, J=7.6 Hz), 4.21 (2H, s), 8.09 (1H, dd, J=1.4, 8.4 Hz), 8.34 (1H, d, J=1.4 Hz), 8.38 (1H, d, J=8.4 Hz), 8.69 (3H, bs).
- Example 77
- 20 3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxamide hydrochloride (1) A solution of 4-butoxy-3-{{(tert-butoxycarbonyl)amino)methyl}-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid (Example 76 (1)) (0.45 g, 3.5 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.38 g, 2 mmol) and 1-hydroxybenzotriazole ammonium salt (0.30 g, 2 mmol) in N,N-dimethylformamide (10 ml) was stirred at room temperature for 3 h. The reaction mixture was
- 25 poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate - diisopropyl ether to give tert-butyl {{(6-aminocarbonyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.35 g, 79.5%) as

crystals.

Melting point 159-160°C.

Elemental analysis for C₂₄H₃₅N₃O₅

Calculated: C, 64.70; H, 7.92; N, 9.43.

5 Found: C, 64.53; H, 8.01; N, 9.53.

¹H-NMR(CDCl₃) δ: 0.96 (6H, d, J=7.0 Hz), 1.03 (3H, t, J=7.3 Hz), 1.48 (9H, s), 1.49-1.63 (2H, m), 1.80-1.95 (2H, m), 2.10-2.21 (1H, m), 3.87 (2H, t, J=6.4 Hz), 4.00 (2H, d, J=7.2 Hz), 4.52 (2H, d, J=5.6 Hz), 5.07 (1H, bs), 10 5.99 (1H, bs), 6.48 (1H, bs), 7.75 (1H, d, J=8.0 Hz), 8.10 (1H, s), 8.35 (1H, d, J=8.0 Hz).

(2) 3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxamide hydrochloride

(synthesized according to the method similar to that in

15 Example 1 (7))

Melting point 171-173°C.

Elemental analysis for C₁₉H₂₈N₃O₃Cl H₂O

Calculated: C, 57.06; H, 7.56; N, 10.51.

Found: C, 57.41; H, 7.62; N, 10.59.

20 ¹H-NMR(DMSO-d₆) δ: 0.89 (6H, d, J=7.0 Hz), 1.01 (3H, t, J=7.3 Hz), 1.48-1.66 (2H, m), 1.80-2.07 (3H, m), 3.94-4.00 (4H, m), 4.20 (2H, s), 7.70 (1H, s), 8.04 (1H, dd, J=1.6, 8.4 Hz), 8.22 (1H, d, J=1.6 Hz), 8.33 (1H, d, J=8.4 Hz), 8.35 (1H, s), 8.60 (3H, bs).

25 Example 78

3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarbonitrile hydrochloride

(1) A solution of tert-butyl {(6-aminocarbonyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-

30 isoquinolinyl)methylcarbamate (Example 77 (1)) (0.54 g, 1.2 mmol) and cyanuric chloride (0.66 g, 3.6 mmol) in N,N-dimethylformamide (10 mmol) was stirred at 0°C for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed

35 with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was

recrystallized from ethyl acetate - n-hexane to give tert-butyl (4-butoxy-6-cyano-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.41 g, 80.4%) as crystals.

5 Melting point 126-127°C.

¹H-NMR(CDCl₃) δ: 0.97 (6H, d, J=6.6 Hz), 1.05 (3H, t, J=7.3 Hz), 1.47 (9H, s), 1.48-1.67 (2H, m), 1.82-1.96 (2H, m), 2.11-2.25 (1H, m), 3.86 (2H, t, J=6.4 Hz), 4.02 (2H, d, J=7.0 Hz), 4.53 (2H, d, J=5.2 Hz), 4.73 (1H, bs), 10 7.68 (1H, d, J=8.0 Hz), 8.01 (1H, s), 8.50 (1H, d, J=8.0 Hz).

(2) 3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarbonitrile hydrochloride (synthesized according to the method similar to that in

15 Example 1 (7))

Melting point 135-136°C.

¹H-NMR(DMSO-d₆) δ: 0.89 (6H, d, J=6.6 Hz), 1.00 (3H, t, J=7.2 Hz), 1.41-1.64 (2H, m), 1.81-1.91 (2H, m), 1.99-2.08 (1H, m), 3.93-4.02 (4H, m), 4.20 (2H, s), 7.99 (1H, d, J=8.2 Hz), 8.24 (1H, s), 8.42 (1H, d, J=8.2 Hz), 8.74 (3H, bs).

Example 79

3-(Aminomethyl)-4-butoxy-6-hydroxymethyl-2-isobutyl-1(2H)-isoquinoline hydrochloride

25 (1) To a solution of 4-butoxy-3-{{(tert-butoxycarbonyl)-amino}methyl}-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 76 (1)) (0.45 g, 3.5 mmol) and N-methylmorpholine (0.13 ml, 1.2 mmol) in

30 tetrahydrofuran (10 ml) was added ethyl chloroformate (0.12 ml, 1.2 mmol) at 0°C, and the mixture was stirred at 0°C for 10 min. To the obtained mixture was added sodium tetrahydroborate (0.11 g, 3 mmol) and the mixture was stirred at 0°C for 1 h. The reaction mixture was

35 poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous

magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate - diisopropyl ether to give tert-butyl (4-butoxy-6-hydroxymethyl-2-isobutyl-1-oxo-1,2-dihydro-3-⁵ isoquinolinyl)methylcarbamate (0.33 g, 76.7%) as crystals.

Melting point 153-154°C.

Elemental analysis for C₂₄H₃₆N₂O₅

Calculated: C, 66.64; H, 8.39; N, 6.48.

¹⁰ Found: C, 66.61; H, 8.21; N, 6.44.

¹H-NMR(CDCl₃) δ: 0.95 (6H, d, J=6.6 Hz), 1.01 (3H, t, J=7.4 Hz), 1.40-1.57 (11H, m), 1.78-1.92 (2H, m), 2.11-2.24 (1H, m), 3.80 (2H, t, J=6.8 Hz), 3.97 (2H, d, J=7.8 Hz), 4.50 (2H, d, J=5.4 Hz), 4.82 (2H, s), 5.25 (1H, bs), 7.39-7.51 (2H, m), 8.17-8.21 (1H, m).

¹⁵ (2) 3-(Aminomethyl)-4-butoxy-6-hydroxymethyl-2-isobutyl-1(2H)-isoquinoline hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Elemental analysis for C₁₉H₂₉N₂O₃Cl 1/2H₂O

²⁰ Calculated: C, 60.39; H, 8.00; N, 7.41.

Found: C, 60.00; H, 7.07; N, 7.07.

¹H-NMR(DMSO-d₆) δ: 0.87 (6H, d, J=6.4 Hz), 1.00 (3H, t, J=7.1 Hz), 1.51-1.62 (2H, m), 1.82-2.02 (3H, m), 3.91-3.99 (4H, m), 4.69 (2H, d, J=5.2 Hz), 5.30 (2H, s), 5.53 (1H, bs), 7.52-7.62 (1H, m), 7.74 (1H, s), 8.21-8.30 (1H, m), 8.64 (3H, bs).

Example 80

N-{3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl}-N'-methylurea hydrochloride

³⁰ (1) A solution of 4-butoxy-3-{{(tert-butoxycarbonyl)amino}methyl}-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 76 (1)) (0.45 g, 1 mmol), diphenylphosphoryl azide (0.26 ml,

³⁵ 1.2 mmol) and triethylamine (0.17 ml, 1.2 mmol) in N,N-dimethylformamide (10 ml) was stirred at room

temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in toluene (20 ml) and the mixture was refluxed with stirring for 1 h. To the obtained mixture was added a solution of 2N methylamine in tetrahydrofuran (1 ml, 2 mmol), and the mixture was refluxed with stirring for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from tetrahydrofuran - diisopropyl ether to give tert-butyl {4-butoxy-2-isobutyl-6-{{(methylamino)carbonyl}-amino}-1-oxo-1,2-dihydro-3-isoquinolinyl}methylcarbamate (0.39 g, 83.0%) as an amorphous.

Elemental analysis for C₂₅H₃₈N₄O₅

Calculated: C, 63.27; H, 8.07; N, 11.81.

Found: C, 62.96; H, 8.35; N, 11.55.

¹H-NMR(CDCl₃) δ: 0.93 (6H, d, J=5.8 Hz), 0.95 (3H, t, J=6.6 Hz), 1.45-1.54 (11H, m), 1.64-1.82 (2H, m), 2.05-2.17 (1H, m), 2.86 (3H, d, J=4.4 Hz), 3.83 (2H, t, J=6.5 Hz), 3.98 (2H, d, J=7.4 Hz), 4.50 (2H, d, J=5.2 Hz), 5.02 (1H, bs), 5.98 (1H, bs), 6.99-7.04 (2H, m), 8.06-8.10 (1H, m), 8.39 (1H, s).

(2) N-{3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl}-N'-methylurea hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 181-183°C.

Elemental analysis for C₂₀H₃₁N₄O₃Cl 1/2H₂O

Calculated: C, 57.20; H, 7.68; N, 13.34.

Found: C, 57.13; H, 7.66; N, 13.40.

¹H-NMR(DMSO-d₆) δ: 0.87 (6H, d, J=6.6 Hz), 0.99 (3H, t, J=7.1 Hz), 1.46-1.65 (2H, m), 1.78-2.07 (3H, m), 3.87-

3.93 (4H, m), 4.14 (2H, d, J=4.6 Hz), 6.74 (1H, bs),
 7.48 (1H, dd, J=2.0, 8.8 Hz), 8.04 (1H, d, J=2.0 Hz),
 8.10 (1H, d, J=8.8 Hz), 8.53 (3H, bs), 9.60 (1H, s).

Example 81

- ⁵ Methyl 3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinylcarbamate hydrochloride
 (1) Methyl 4-butoxy-3-{{(tert-butoxycarbonyl)amino}-methyl}-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinylcarbamate (synthesized according to the

¹⁰ method similar to that in Example 80 (1))

Elemental analysis for C₂₅H₃₈N₄O₅

Calculated: C, 63.14; H, 7.84; N, 8.84.

Found: C, 62.99; H, 7.87; N, 9.01.

- ¹⁵ ¹H-NMR(CDCl₃) δ: 0.95 (6H, d, J=7.0 Hz), 1.03 (3H, t, J=7.1 Hz), 1.46 (9H, s), 1.52-1.67 (2H, m), 1.81-1.95 (2H, m), 2.09-2.23 (1H, m), 3.82 (3H, s), 3.88 (2H, t, J=6.6 Hz), 3.98 (2H, d, J=7.4 Hz), 4.51 (2H, d, J=5.4 Hz), 4.80 (1H, bs), 7.09 (1H, bs), 7.36 (1H, dd, J=2.0, 8.8 Hz), 7.89 (1H, d, J=2.0 Hz), 8.33 (1H, d, J=8.8 Hz).

- ²⁰ (2) Methyl 3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinylcarbamate hydrochloride (synthesized according to the method similar to that in Example 1 (7)).

Melting point 166-168°C.

- ²⁵ Elemental analysis for C₂₀H₃₀N₃O₄Cl 1/4H₂O

Calculated: C, 57.69; H, 7.38; N, 10.09.

Found: C, 57.59; H, 7.66; N, 10.02.

- ²⁵ ¹H-NMR(DMSO-d₆) δ: 0.87 (6H, d, J=6.6 Hz), 1.00 (3H, t, J=7.4 Hz), 1.47-1.65 (2H, m), 1.79-2.04 (3H, m), 3.73 (3H, s), 3.89-3.94 (4H, m), 4.15 (2H, d, J=4.6 Hz), 7.63 (1H, dd, J=1.8, 8.8 Hz), 8.03 (1H, d, J=1.8 Hz), 8.17 (1H, d, J=8.8 Hz), 8.62 (3H, bs), 10.28 (1H, s).

Example 82

- 6-Amino-3-(aminomethyl)-4-butoxy-2-isobutyl-1(2H)-isoquinolinone dihydrochloride
 (1) A solution of 4-butoxy-3-{{(tert-

butoxycarbonyl)amino}methyl}-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 76 (1)) (0.45 g, 1 mmol), diphenylphosphoryl azide (0.26 ml, 5 1.2 mmol) and triethylamine (0.17 ml, 1.2 mmol) in N,N-dimethylformamide (10 ml) was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in toluene (20 ml) and the mixture was refluxed with stirring for 1 h. To the obtained mixture was added 9H-fluorenylmethanol (0.29 g, 1.5 mmol) and the mixture was refluxed with stirring for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography 10 and recrystallized from tetrahydrofuran - diisopropyl ether to give 9H-fluoren-9-ylmethyl 4-butoxy-3-{{(tert-butoxycarbonyl)amino}methyl}-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinylcarbamate (0.53 g, 82.8%) as crystals.

15 Melting point 137-138°C.
Elemental analysis for C₃₈H₄₅N₃O₆
Calculated: C, 71.34; H, 7.09; N, 6.57.
Found: C, 71.09; H, 7.03; N, 6.63.
¹H-NMR(CDCl₃) δ: 0.95 (6H, d, J=7.0 Hz), 1.01 (3H, t, J=7.4 Hz), 1.46 (9H, s), 1.47-1.61 (2H, m), 1.79-1.90 (2H, m), 2.09-2.23 (1H, m), 3.85 (2H, t, J=6.4 Hz), 3.97 (2H, d, J=7.4 Hz), 4.28 (1H, t, J=6.2 Hz), 4.50 (2H, d, J=5.2 Hz), 4.61 (2H, d, J=6.2 Hz), 4.80 (2H, bs), 7.11-7.16 (1H, m), 7.29-7.46 (4H, m), 7.63 (2H, d, J=7.0 Hz), 30 7.79 (2H, d, J=7.0 Hz), 7.87 (1H, d, J=1.8 Hz), 8.32 (1H, d, J=8.8 Hz).

(2) To a solution of 9H-fluoren-9-ylmethyl 4-butoxy-3-{{(tert-butoxycarbonyl)amino}methyl}-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinylcarbamate (0.45 g, 0.7 mmol) in N,N-dimethylformamide (10 ml) was added pyrrolidine
⁵ (0.5 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was
¹⁰ purified by silica gel column chromatography to give tert-butyl (6-amino-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.23 g, 79.3%) as crystals.

Melting point 175-176°C.

¹⁵ Elemental analysis for C₂₃H₃₅N₃O₄

Calculated: C, 66.16; H, 8.45; N, 10.06.

Found: C, 66.10; H, 8.74; N, 10.05.

¹H-NMR(CDCl₃) δ: 0.94 (6H, d, J=6.6 Hz), 1.02 (3H, t, J=7.4 Hz), 1.46 (9H, s), 1.50-1.64 (2H, m), 1.77-1.91

²⁰ (2H, m), 2.05-2.22 (1H, m), 3.82 (2H, t, J=6.6 Hz), 3.93 (2H, d, J=7.2 Hz), 4.16 (2H, s), 4.47 (2H, d, J=5.4 Hz), 4.69 (1H, bs), 6.778-6.83 (2H, m), 8.21 (1H, d, J=9.2 Hz).

(3) 6-Amino-3-(aminomethyl)-4-butoxy-2-isobutyl-1(2H)-
²⁵ isoquinolinone dihydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 245-247°C.

Elemental analysis for C₁₈H₂₉N₃O₂Cl₂

Calculated: C, 55.38; H, 7.49; N, 10.76.

³⁰ Found: C, 55.02; H, 7.47; N, 10.72.

¹H-NMR(DMSO-d₆) δ: 0.86 (6H, d, J=6.6 Hz), 0.99 (3H, t, J=7.4 Hz), 1.44-1.63 (2H, m), 1.77-2.02 (3H, m), 3.84-3.90 (4H, m), 4.11 (2H, d, J=4.0 Hz), 6.30 (3H, bs), 6.91-7.01 (2H, m), 8.00 (1H, d, J=9.2 Hz), 8.60 (3H, bs).

³⁵ Example 83

3-(Aminomethyl)-6-bromo-4-butoxy-2-neopentyl-1(2H)-

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similar to that in Example 4 (4))

Melting point 162-163°C.

Elemental analysis for C₁₉H₂₆NO₃Br

Calculated: C, 57.58; H, 6.61; N, 3.53.

⁵ Found: C, 57.60; H, 6.55; N, 3.49.

¹H-NMR(CDCl₃) δ:0.95 (9H, s), 1.05 (3H, t, J=7.1 Hz), 1.51-1.69 (2H, m), 1.80-1.93 (2H, m), 2.88 (1H, t, J=5.8 Hz), 3.88 (2H, t, J=6.4 Hz), 4.18 (2H, bs), 4.86 (2H, bs), 7.49 (1H, dd, J=1.8, 8.8 Hz), 7.75 (1H, d, J=1.8

¹⁰ Hz), 8.08 (1H, d, J=8.8 Hz).

(5) 6-Bromo-4-butoxy-3-chloromethyl-2-neopentyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

¹H-NMR(CDCl₃) δ:0.98 (9H, s), 1.05 (3H, t, J=7.3 Hz), 1.52-1.70 (2H, m), 1.82-1.95 (2H, m), 3.94 (2H, t, J=6.4 Hz), 4.18 (2H, bs), 4.86 (2H, bs), 7.67 (1H, dd, J=1.8, 8.8 Hz), 7.87 (1H, d, J=1.8 Hz), 8.28 (1H, d, J=8.8 Hz).

(6) 2-{(6-Bromo-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl}-1H-isoindole-1,3(2H)-dione

²⁰ (synthesized according to the method similar to that in Example 4 (6))

Melting point 134-136°C.

Elemental analysis for C₂₇H₂₉N₂O₄Br

Calculated: C, 61.72; H, 5.56; N, 5.33.

²⁵ Found: C, 61.92; H, 5.49; N, 5.32.

¹H-NMR(CDCl₃) δ:1.02 (9H, s), 1.02 (3H, t, J=7.3 Hz), 1.46-1.65 (2H, m), 1.82-1.96 (2H, m), 4.01 (2H, t, J=6.8 Hz), 4.05 (2H, bs), 5.07 (2H, s), 7.58 (1H, dd, J=2.0, 8.6 Hz), 7.60-7.84 (4H, m), 7.87 (1H, d, J=2.0 Hz), 8.25

³⁰ (1H, d, J=8.6 Hz).

(7) Tert-butyl (6-bromo-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 1 (6))

³⁵ Melting point 130-131°C.

Elemental analysis for C₂₄H₃₅N₂O₄Br

Calculated: C, 58.18; H, 7.12; N, 5.65.

Found: C, 58.50; H, 7.09; N, 5.56.

¹H-NMR(CDCl₃) δ: 0.99 (9H, s), 1.04 (3H, t, J=7.4 Hz), 1.45 (9H, s), 1.46-1.68 (2H, m), 1.80-1.93 (2H, m), 3.85 (2H, t, J=6.4 Hz), 4.14 (2H, bs), 4.56 (2H, d, J=5.4 Hz), 4.71 (1H, bs), 7.58 (1H, dd, J=1.8, 8.4 Hz), 7.82 (1H, d, J=1.8 Hz), 8.24 (1H, d, J=8.4 Hz).

(8) 3-(Aminomethyl)-6-bromo-4-butoxy-2-neopentyl-1(2H)-isoquinolinone hydrochloride (synthesized according to

¹⁰ the method similar to that in Example 1 (7))

Melting point 114-115°C.

Elemental analysis for C₁₉H₂₈N₂O₂BrCl

Calculated: C, 52.85; H, 6.54; N, 6.49.

Found: C, 52.60; H, 6.62; N, 6.44...

¹⁵ ¹H-NMR(DMSO-d₆) δ: 0.90 (9H, s), 1.00 (3H, t, J=7.4 Hz), 1.46-1.64 (2H, m), 1.77-1.90 (2H, m), 3.94 (2H, t, J=6.0 Hz), 4.12 (2H, bs), 4.24 (2H, s), 7.79 (1H, dd, J=1.8, 8.4 Hz), 7.87 (1H, d, J=1.8 Hz), 8.19 (1H, d, J=8.4 Hz), 8.52 (3H, bs).

²⁰ Example 84

Methyl 3-(aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isouquinolinecarboxylate hydrochloride

(1) Methyl 4-butoxy-3-{{(tert-butoxycarbonyl)amino)methyl}-2-neopentyl-1-oxo-1,2-

²⁵ dihydro-6-isouquinolinecarboxylate (synthesized according to the method similar to that in Example 75 (1))

Elemental analysis for C₂₆H₃₈N₂O₆

Calculated: C, 65.80; H, 8.07; N, 5.90..

Found: C, 66.03; H, 8.33; N, 6.05.

³⁰ ¹H-NMR(CDCl₃) δ: 1.00 (9H, s), 10.6 (3H, t, J=7.4 Hz), 1.46 (9H, s), 1.53-1.71 (2H, m), 1.83-1.97 (2H, m), 3.90 (2H, t, J=6.4 Hz), 3.99 (3H, s), 4.14 (2H, bs), 4.59 (2H, d, J=5.4 Hz), 4.79 (1H, bs), 8.06 (1H, dd, J=1.7, 8.4 Hz), 8.38 (1H, d, J=1.7 Hz), 8.43 (1H, d, J=8.4 Hz).

³⁵ (2) Methyl 3-(aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isouquinolinecarboxylate hydrochloride

(synthesized according to the method similar to that in Example 1 (7))

Melting point 123-124°C.

Elemental analysis for C₂₁H₃₁N₂O₄Cl

⁵ Calculated: C, 61.38; H, 7.60; N, 6.82.

Found: C, 61.08; H, 7.82; N, 6.82.

¹H-NMR(DMSO-d₆) δ:0.92 (9H, s), 1.02 (3H, t, J=7.3 Hz), 1.55-1.66 (2H, m), 1.79-1.91 (2H, m), 3.95 (3H, s), 3.97 (2H, t, J=6.2 Hz), 4.14 (2H, bs), 4.28 (2H, s), 8.11 (1H, dd, J=1.6, 8.6 Hz), 8.34 (1H, d, J=1.6 Hz), 8.40 (1H, d, J=8.6 Hz), 8.56 (3H, bs).

Example 85

3-(Aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid hydrochloride

¹⁵ (1) 4-Butoxy-3-{{(tert-butoxycarbonyl)amino}methyl}-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 76 (1))

Melting point 130-131°C.

²⁰ Elemental analysis for C₂₅H₃₆N₂O₆

Calculated: C, 65.20; H, 7.88; N, 6.08.

Found: C, 64.92; H, 7.88; N, 6.04.

¹H-NMR(CDCl₃) δ:0.99 (9H, s), 1.08 (3H, t, J=7.3 Hz), 1.50 (9H, s), 1.56-1.73 (2H, m), 1.85-1.99 (2H, m), 3.90 (2H, t, J=6.2 Hz), 4.14 (2H, bs), 4.61 (2H, d, J=5.2 Hz), 5.64 (1H, bs), 8.31 (1H, d, J=8.4 Hz), 8.28-8.33 (2H, m).

²⁵ (2) 3-(Aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid hydrochloride (synthesized according to the method similar to that in

³⁰ Example 1 (7))

Melting point 255-257°C.

Elemental analysis for C₂₀H₂₉N₂O₄Cl

Calculated: C, 60.52; H, 7.36; N, 7.06.

Found: C, 60.42; H, 7.35; N, 7.01.

³⁵ ¹H-NMR(DMSO-d₆) δ:0.92 (9H, s), 1.01 (3H, t, J=7.4 Hz), 1.54-1.66 (2H, m), 1.79-1.92 (2H, m), 3.97 (2H, t, J=6.3

Hz), 4.13 (2H, bs), 4.28 (2H, s), 8.09 (1H, dd, J=1.5, 8.4 Hz), 8.33 (1H, bs), 8.34 (1H, d, J=1.5 Hz), 8.38 (1H, d, J=8.4 Hz), 8.60 (3H, bs).

Example 86

⁵ 3-(Aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isouquinolinecarboxamide hydrochloride

(1) Tert-butyl ((6-aminocarbonyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isouquinolinyl)methylcarbamate
(synthesized according to the method similar to that in

¹⁰ Example 77 (1))

Melting point 172-173°C.

Elemental analysis for C₂₅H₃₇N₃O₅ 1/2(i-Pr)₂O

Calculated: C, 65.86; H, 8.49; N, 8.23.

Found: C, 65.53; H, 8.75; N, 8.17. . .

¹⁵ ¹H-NMR(CDCl₃) δ: 0.99 (9H, s), 1.04 (3H, t, J=7.2 Hz), 1.46 (9H, s), 1.47-1.68 (2H, m), 1.81-1.95 (2H, m), 3.71 (2H, t, J=6.2 Hz), 4.14 (2H, bs), 4.58 (2H, d, J=5.6 Hz), 4.97 (1H, bs), 5.91 (1H, bs), 6.39 (1H, bs), 7.75 (1H, dd, J=1.6, 8.4 Hz), 8.12 (1H, d, J=8.4 Hz), 8.36 (1H, d, J=8.4 Hz).

²⁰ (2) 3-(Aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isouquinolinecarboxamide hydrochloride
(synthesized according to the method similar to that in Example 1 (7))

²⁵ Melting point 237-238°C.

Elemental analysis for C₂₀H₃₀N₃O₃Cl 1/2H₂O

Calculated: C, 59.32; H, 7.72; N, 10.38.

Found: C, 59.45; H, 7.63; N, 10.20.

¹H-NMR(DMSO-d₆) δ: 0.91 (9H, s), 1.00 (3H, t, J=7.4 Hz),

³⁰ 1.48-1.67 (2H, m), 1.80-1.92 (2H, m), 3.98 (2H, t, J=6.4 Hz), 4.12 (2H, bs), 4.26 (2H, s), 7.70 (1H, s), 8.04 (1H, dd, J=1.2, 8.2 Hz), 8.22 (1H, d, J=1.2 Hz), 8.33 (1H, d, J=8.2 Hz), 8.37 (1H, s), 8.58 (3H, bs).

Example 87

³⁵ 3-(Aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isouquinolinecarbonitrile hydrochloride

(1) Tert-butyl (4-butoxy-6-cyano-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 78 (7))

5 Melting point 162-163°C.

Elemental analysis for C₂₅H₃₅N₃O₄

Calculated: C, 68.00; H, 7.99; N, 9.52.

Found: C, 67.97; H, 8.13; N, 9.44.

¹H-NMR(CDCl₃) δ: 1.00 (9H, s), 1.05 (3H, t, J=7.3 Hz),

10 1.45 (9H, s), 1.53-1.68 (2H, m), 1.82-1.90 (2H, m), 3.86 (2H, t, J=6.6 Hz), 4.17 (2H, bs), 4.58 (2H, d, J=5.4 Hz), 4.70 (1H, bs), 7.68 (1H, dd, J=1.6, 8.8 Hz), 8.00 (1H, d, J=1.6 Hz), 8.49 (1H, d, J=8.2 Hz).

(2) 3-(Aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-

15 dihydro-6-isoquinolinecarbonitrile hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Elemental analysis for C₂₀H₂₈N₃O₂Cl 1/4H₂O

Calculated: C, 62.81; H, 7.51; N, 10.99.

20 Found: C, 62.98; H, 7.75; N, 10.95.

¹H-NMR(DMSO-d₆) δ: 0.91 (9H, s), 1.00 (3H, t, J=7.1 Hz), 1.46-1.64 (2H, m), 1.80-1.92 (2H, m), 3.97 (2H, t, J=6.4 Hz), 4.14 (2H, bs), 4.27 (2H, bs), 7.97 (1H, dd, J=1.2, 8.0 Hz), 8.23 (1H, d, J=1.2 Hz), 8.41 (1H, d, J=8.0 Hz),

25 8.68 (3H, bs).

Example 88

N-{3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl}acetamide hydrochloride

(1) A solution of tert-butyl (6-amino-4-butoxy-2-

30 isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 82 (2)) (0.21 g, 0.5 mmol) and acetyl chloride (0.04 ml, 0.6 mmol) in N,N-dimethylacetamide (10 ml) was stirred at room

35 temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The

extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate - diisopropyl ether to give tert-butyl {6-(acetylamino)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl}methylcarbamate (0.19 g, 80.8%) as crystals.

⁵ Melting point 174-175°C.

Elemental analysis for C₂₅H₃₇N₃O₅

¹⁰ Calculated: C, 65.34; H, 8.11; N, 9.14.

Found: C, 65.32; H, 8.05; N, 9.21.

¹H-NMR(CDCl₃) δ: 0.95 (6H, d, J=6.6 Hz), 1.02 (3H, t, J=7.4 Hz), 1.47 (9H, s), 1.47-1.65 (2H, m), 1.81-1.95 (2H, m), 2.09-2.20 (1H, m), 2.26 (3H, s), 3.88 (2H, t, J=6.6 Hz); 3.98 (2H, d, J=7.4 Hz), 4.51 (2H, d, J=5.6 Hz), 4.82 (1H, bs), 7.35 (1H, d, J=8.0 Hz), 7.71 (1H, bs), 8.17 (1H, s), 8.32 (1H, d, J=8.0 Hz).

(2) N-{3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl}acetamide hydrochloride

¹⁵ ²⁰ synthesized according to the method similar to that in Example 1 (7))

Melting point 176-177°C.

Elemental analysis for C₂₀H₃₀N₃O₃Cl H₂O

Calculated: C, 58.03; H, 7.79; N, 10.15.

²⁵ Found: C, 58.26; H, 8.11; N, 10.08.

¹H-NMR(DMSO-d₆) δ: 0.87 (6H, d, J=6.6 Hz); 0.99 (3H, t, J=7.3 Hz), 1.50-1.62 (2H, m), 1.79-2.04 (3H, m), 2.14 (3H, s), 3.91 (2H, t, J=6.8 Hz), 3.93 (2H, d, J=7.0 Hz), 4.16 (2H, d, J=5.4 Hz), 7.70 (1H, dd, J=2.0, 8.8 Hz),

³⁰ 8.18 (1H, d, J=8.8 Hz), 8.27 (1H, d, J=2.0 Hz), 8.56 (3H, bs), 10.59 (1H, s).

Example 89

N-{3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl}propanamide hydrochloride

³⁵ (1) tert-butyl {4-butoxy-2-isobutyl-1-oxo-6-(propionylamino)-1,2-dihydro-3-

isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 88 (1))

¹H-NMR(CDCl₃) δ: 0.95 (6H, d, J=7.0 Hz), 1.01 (3H, t, J=7.2 Hz), 1.28 (3H, t, J=7.6 Hz), 1.46 (9H, s), 1.47-

⁵ 1.67 (2H, m), 1.80-1.94 (2H, m), 2.09-2.27 (1H, m), 2.48 (2H, q, J=7.6 Hz), 3.88 (2H, t, J=6.4 Hz), 3.98 (2H, d, J=7.4 Hz), 4.51 (2H, d, J=5.0 Hz), 4.83 (1H, bs), 7.37 (1H, dd, J=1.8, 8.8 Hz), 7.69 (1H, bs), 8.15 (1H, d, J=1.8 Hz), 8.31 (1H, d, J=8.8 Hz).

¹⁰ (2) N-{3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl}propanamide hydrochloride (synthesized according to the method similar to that in Example 1 (7)).

¹H-NMR(DMSO-d₆) δ: 0.87 (6H, d, J=7.0 Hz), 1.00 (6H, m), ¹⁵ 1.46-1.64 (2H, m), 1.72-2.14 (3H, m), 2.41-2.50 (2H, m), 3.91 (4H, bs), 4.16 (2H, s), 7.72 (1H, d, J=9.0 Hz), 8.18 (1H, d, J=9.0 Hz), 8.27 (1H, s), 8.55 (3H, bs), 10.49 (1H, s).

Example 90

²⁰ N-{3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl}-2-methylpropanamide hydrochloride

(1) Tert-butyl {4-butoxy-2-isobutyl-6-(isobutyrylamino)-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate

²⁵ (synthesized according to the method similar to that in Example 88 (1))

¹H-NMR(CDCl₃) δ: 0.95 (6H, d, J=7.0 Hz), 1.02 (3H, t, J=7.2 Hz), 1.29 (6H, d, J=7.0 Hz), 1.46 (9H, s), 1.47-1.66 (2H, m), 1.80-1.91 (2H, m), 2.09-2.20 (1H, m),

³⁰ 2.53-2.66 (1H, m), 3.89 (2H, t, J=6.6 Hz), 3.98 (2H, d, J=7.4 Hz), 4.51 (2H, d, J=5.6 Hz), 4.79 (1H, bs), 7.41 (1H, dd, J=1.8, 8.8 Hz), 7.62 (1H, bs), 8.15 (1H, d, J=1.8 Hz), 8.32 (1H, d, J=8.8 Hz).

(2) N-{3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-

³⁵ dihydro-6-isoquinolinyl}-2-methylpropanamide hydrochloride (synthesized according to the method

similar to that in Example 1 (7))

Melting point 181-183°C.

¹H-NMR(DMSO-d₆) δ:0.88 (6H, d, J=6.2 Hz), 1.00 (3H, t, J=7.4 Hz), 1.14 (6H, d, J=6.6 Hz), 1.48-1.64 (2H, m), 1.83-2.12 (3H, m), 2.62-2.78 (1H, m), 3.92-3.95 (4H, m), 4.16 (2H, bs), 7.76 (1H, d, J=8.8 Hz), 8.18 (1H, d, J=8.8 Hz), 8.27 (1H, s), 8.57 (3H, bs), 10.47 (1H, s).

Example 91

N-{3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-

¹⁰ dihydro-6-isoquinolinyl}benzamide hydrochloride
(1) Tert-butyl {4-butoxy-6-(benzoylamino)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl}methylcarbamate
(synthesized according to the method similar to that in Example 88 (1))

¹⁵ ¹H-NMR(CDCl₃) δ:0.95 (6H, d, J=6.6 Hz), 1.02 (3H, t, J=7.4 Hz), 1.47 (9H, s), 1.48-1.68 (2H, m), 1.82-1.96 (2H, m), 2.07-2.23 (1H, m), 3.92 (2H, t, J=6.8 Hz), 3.98 (2H, d, J=8.8 Hz), 4.52 (2H, d, J=5.4 Hz), 4.89 (1H, bs), 7.45-7.62 (4H, m), 7.90-7.94 (2H, m), 8.25 (1H, bs), 7.56 (1H, bs), 8.27 (1H, d, J=1.8 Hz), 8.32 (1H, d, J=8.8 Hz).

²⁰ (2) N-{3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl}benzamide hydrochloride
(synthesized according to the method similar to that in

²⁵ Example 1 (7))

¹H-NMR(DMSO-d₆) δ:0.89 (6H, d, J=6.6 Hz), 1.01 (3H, t, J=7.3 Hz), 1.49-1.67 (2H, m), 1.83-2.06 (3H, m), 3.93-3.98 (4H, m), 4.19 (2H, s), 7.54-7.68 (3H, m), 7.95-8.03 (3H, m), 8.25 (1H, d, J=8.8 Hz), 8.43 (1H, d, J=1.8 Hz), 8.58 (3H, bs), 10.77 (1H, s).

Example 92

N-{3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl}cyclopentanecarboxamide hydrochloride

³⁵ (1) Tert-butyl {4-butoxy-6-((cyclopentylcarbonyl)amino)-2-isobutyl-1-oxo-1,2-dihydro-3-

isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 88 (1))

¹H-NMR(CDCl₃) δ: 0.95 (6H, d, J=7.0 Hz), 1.02 (3H, t, J=7.3 Hz), 1.46 (9H, s), 1.47-1.74 (4H, m), 1.78-2.20

⁵ (9H, m), 2.67-2.80 (1H, m), 3.89 (2H, t, J=6.6 Hz), 3.98 (2H, d, J=7.6 Hz), 4.51 (2H, d, J=5.4 Hz), 4.78 (1H, bs), 7.42 (1H, dd, J=2.2, 8.8 Hz), 7.56 (1H, bs), 8.12 (1H, d, J=2.2 Hz), 8.32 (1H, d, J=8.8 Hz).

(2) N-{3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl)cyclopentanecarboxamide
(synthesized according to the method similar to that in Example 1 (7))

¹H-NMR(DMSO-d₆) δ: 0.87 (6H, d, J=6.2 Hz), 0.99 (3H, t, J=7.1 Hz), 1.54-2.11 (11H, m), 2.79-2.92 (1H, m), 3.91-

¹⁵ 3.95 (4H, m); 4.16 (2H, s), 7.75 (1H, d, J=8.8 Hz), 8.18 (1H, d, J=8.8 Hz), 8.25 (1H, s), 8.55 (3H, bs), 10.49 (1H, s).

Example 93

N-{3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl)methanesulfonamide hydrochloride
(1) Tert-butyl {4-butoxy-2-isobutyl-6-((methylsulfonyl)amino)-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 88 (1))

²⁵ ¹H-NMR(CDCl₃) δ: 0.95 (6H, d, J=6.6 Hz), 1.02 (3H, t, J=7.4 Hz), 1.47 (9H, s), 1.47-1.64 (2H, m), 1.79-1.94 (2H, m), 2.10-2.23 (1H, m), 3.11 (3H, s), 3.86 (2H, t, J=6.6 Hz), 3.99 (2H, d, J=7.8 Hz), 4.51 (2H, d, J=5.4 Hz), 4.77 (1H, bs), 7.23 (1H, dd, J=2.0, 8.6 Hz), 7.31 (1H, s), 7.56 (1H, d, J=2.0 Hz), 8.38 (1H, d, J=8.6 Hz).

³⁰ (2) N-{3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl)methanesulfonamide (synthesized according to the method similar to that in Example 1 (7))

³⁵ ¹H-NMR(DMSO-d₆) δ: 0.87 (6H, d, J=6.6 Hz), 0.99 (3H, t, J=7.8 Hz), 1.45-1.64 (2H, m), 1.78-2.09 (3H, m), 3.13

(3H, s), 3.88-3.94 (4H, m), 4.17 (2H, bs), 7.40 (1H, dd, J=2.0, 8.8 Hz), 7.60 (1H, d, J=2.0 Hz), 8.21 (1H, d, J=8.8 Hz), 8.58 (3H, bs), 10.57 (1H, s).

Example 94

- ⁵ N-{3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl}benzenesulfonamide hydrochloride
 (1) Tert-butyl {4-butoxy-2-isobutyl-1-oxo-6-((phenylsulfonyl)amino)-1,2-dihydro-3-isoquinolinyl}methylcarbamate (synthesized according to

¹⁰ the method similar to that in Example 88 (1))
 Melting point 160-161°C.

Elemental analysis for C₂₉H₃₉N₃O₆S

Calculated: C, 62.45; H, 7.05; N, 7.53.

Found: C, 62.35; H, 6.97; N, 7.50.

- ¹⁵ ¹H-NMR(CDCl₃) δ: 0.93 (6H, d, J=6.6 Hz), 1.02 (3H, t, J=7.3 Hz), 1.46 (9H, s), 1.47-1.63 (2H, m), 1.72-1.90 (2H, m), 2.07-2.20 (1H, m), 3.76 (2H, t, J=6.6 Hz), 3.96 (2H, d, J=7.6 Hz), 4.48 (2H, d, J=5.6 Hz), 4.78 (1H, bs), 7.14 (1H, d, J=8.4 Hz), 7.41-7.58 (4H, m), 7.81-7.99 (3H, m), 8.25 (1H, dd, J=1.4, 8.4 Hz).

- ²⁰ (2) N-{3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl}benzenesulfonamide (synthesized according to the method similar to that in Example 1 (7))

²⁵ Melting point 166-167°C.

Elemental analysis for C₂₄H₃₂N₃O₄ClS 1/4H₂O

Calculated: C, 57.82; H, 6.57; N, 8.43.

Found: C, 57.83; H, 6.49; N, 8.26.

- ¹H-NMR(DMSO-d₆) δ: 0.84 (6H, d, J=7.4 Hz), 1.01 (3H, t, J=7.4 Hz), 1.43-1.62 (2H, m), 1.75-1.99 (3H, m), 3.76 (2H, t, J=6.6 Hz), 3.89 (2H, d, J=6.8 Hz), 4.11 (2H, bs), 7.35 (1H, dd, J=2.0, 8.6 Hz), 7.53-7.65 (3H, m), 7.83-7.88 (2H, m), 8.13 (1H, d, J=8.6 Hz), 8.52 (3H, bs), 11.18 (1H, s).

³⁵ **Example 95**

2-{3-(Aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-

dihydro-6-isoquinolinyl}oxy}acetamide hydrochloride

(1) A solution of tert-butyl (4-butoxy-6-hydroxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (Example 59 (1)) (0.43 g,

5 1 mmol), iodoacetamide (0.22 g, 1.2 mmol) and 1,8-diazabicyclo[5.4.0]-7-undecene (0.18 ml, 1.2 mmol) in N,N-dimethylformamide (10 ml) was stirred at 70°C for 12 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed

10 with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate - diisopropyl ether to give tert-butyl {6-(2-amino-2-oxoethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl}-

15 methylcarbamate (0.29 g, 60.4%) as crystals.

Melting point 114-115°C.

Elemental analysis for C₂₆H₃₉N₃O₆

Calculated: C, 63.78; H, 8.03; N, 8.58.

Found: C, 63.61; H, 7.91; N, 8.43.

20 ¹H-NMR(CDCl₃) δ: 0.99 (9H, s), 1.04 (3H, t, J=7.0 Hz), 1.43 (9H, s), 1.45-1.67 (2H, m), 1.79-1.90 (2H, m), 3.85 (2H, t, J=6.6 Hz), 4.14 (2H, bs), 4.56 (2H, d, J=5.4 Hz), 4.57 (1H, bs), 7.07-7.12 (2H, m), 8.36 (1H, d, J=9.4 Hz). (2) 2-{3-(Aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-

25 dihydro-6-isoquinolinyl}oxy}acetamide hydrochloride (synthesized according to the method similar to that in Example 1 (7)).

Melting point 233-235°C.

Elemental analysis for C₂₁H₃₂N₃O₄Cl 1/2H₂O

30 Calculated: C, 57.99; H, 7.65; N, 9.66.

Found: C, 58.18; H, 7.68; N, 9.63.

¹H-NMR(DMSO-d₆) δ: 0.89 (9H, s), 1.00 (3H, t, J=7.3 Hz), 1.50-1.65 (2H, m), 1.77-1.91 (2H, m), 3.92 (2H, t, J=6.4 Hz), 4.07 (2H, bs), 4.22 (2H, d, J=4.4 Hz), 4.64 (2H, s),

35 7.07 (1H, d, J=2.6 Hz), 7.22 (1H, dd, J=2.6, 8.8 Hz), 7.46 (1H, bs), 7.73 (1H, bs), 8.20 (1H, d, J=8.8 Hz),

8.54 (3H, bs).

Example 96

3-(Aminomethyl)-4-butoxy-6-isopropoxy-2-neopentyl-1(2H)-isoquinolinone hydrochloride

- ⁵ (1) Tert-butyl (4-butoxy-6-isopropoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 95 (1))

Melting point 130-130.5°C.

- ¹⁰ Elemental analysis for C₂₇H₄₂N₂O₅

Calculated: C, 68.32; H, 8.92; N, 5.90.

Found: C, 68.28; H, 8.75; N, 5.99.

¹H-NMR(CDCl₃) δ: 0.99 (9H, s), 1.03 (3H, t, J=7.4 Hz), 1.41 (6H, d, J=5.8 Hz), 1.45 (9H, s), 1.46-1.65 (2H, m),

- ¹⁵ 1.79-1.93 (2H, m), 3.86 (2H, t, J=6.4 Hz), 4.14 (2H, bs), 4.55 (2H, d, J=4.8 Hz), 4.64-4.76 (2H, m), 7.00-7.04 (2H, m), 8.31 (1H, d, J=9.6 Hz).

(2) 3-(Aminomethyl)-4-butoxy-6-isopropoxy-2-neopentyl-1(2H)-isoquinolinone hydrochloride (synthesized

- ²⁰ according to the method similar to that in Example 1 (7))

Melting point 181-182°C.

Elemental analysis for C₂₂H₃₅N₂O₃Cl

Calculated: C, 64.29; H, 8.58; N, 6.82.

- ²⁵ Found: C, 64.10; H, 8.80; N, 6.78.

¹H-NMR(DMSO-d₆) δ: 0.90 (9H, s), 1.00 (3H, t, J=7.1 Hz), 1.35 (6H, d, J=6.2 Hz), 1.51-1.62 (2H, m), 1.77-1.90 (2H, m), 3.93 (2H, t, J=6.3 Hz), 4.07 (2H, bs), 4.22 (2H, bs), 4.74-4.86 (1H, m), 7.05 (1H, d, J=2.4 Hz), 7.16 (1H, dd,

- ³⁰ J=2.4, 8.8 Hz), 8.17 (1H, d, J=8.8 Hz), 8.52 (3H, bs).

Example 97

3-(Aminomethyl)-4-butoxy-2-neopentyl-6-(2,2,2-trifluoroethoxy)-1(2H)-isoquinolinone hydrochloride

- (1) Tert-butyl {4-butoxy-2-neopentyl-6-(2,2,2-

- ³⁵ trifluoroethoxy)-1-oxo-1,2-dihydro-3-isoquinolinyl}methylcarbamate (synthesized according to

the method similar to that in Example 95 (1))

Melting point 154.5-155°C.

Elemental analysis for $C_{26}H_{37}N_2O_5F_3$

Calculated: C, 60.69; H, 7.25; N, 5.44.

⁵ Found: C, 60.44; H, 7.16; N, 5.48.

¹H-NMR(CDCl₃) δ: 0.99 (9H, s), 1.04 (3H, t, J=7.0 Hz), 1.45 (9H, s), 1.46-1.64 (2H, m), 1.80-1.90 (2H, m), 3.86 (2H, t, J=6.6 Hz), 4.11 (2H, bs), 4.48 (2H, q, J=8.0 Hz), 4.56 (2H, d, J=5.6 Hz), 4.71 (1H, bs), 7.09-7.13 (2H, m),

¹⁰ 8.37 (1H, d, J=8.0 Hz).

(2) 3-(Aminomethyl)-4-butoxy-2-neopentyl-6-(2,2,2-trifluoroethoxy)-1(2H)-isoquinolinone hydrochloride
(synthesized according to the method similar to that in Example 1 (7))

¹⁵ Melting point 145.5-146°C.

Elemental analysis for $C_{21}H_{30}N_2O_3ClF_3 \cdot 1/2H_2O$

Calculated: C, 54.84; H, 6.79; N, 6.09.

Found: C, 54.75; H, 6.77; N, 6.22.

¹H-NMR(DMSO-d₆) δ: 0.90 (9H, s), 0.99 (3H, t, J=7.3 Hz),

²⁰ 1.47-1.65 (2H, m), 1.78-1.89 (2H, m), 3.95 (2H, t, J=6.4 Hz), 4.08 (2H, bs), 4.24 (2H, bs), 5.02 (2H, q, J=8.8 Hz), 7.18 (1H, d, J=2.6 Hz), 7.32 (1H, dd, J=2.6, 8.8 Hz), 8.24 (1H, d, J=8.8 Hz), 8.52 (3H, bs).

Example 98

²⁵ 3-(Aminomethyl)-4-butoxy-6-(cyclopropylmethoxy)-2-neopentyl-1(2H)-isoquinolinone hydrochloride

(1) Tert-butyl {4-butoxy-6-(cyclopropylmethoxy)-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to

³⁰ the method similar to that in Example 95 (1))

Melting point 154-155°C.

Elemental analysis for $C_{28}H_{42}N_2O_5 \cdot 1/2H_2O$

Calculated: C, 67.85; H, 8.74; N, 5.65.

Found: C, 68.08; H, 8.65; N, 5.47.

³⁵ ¹H-NMR(CDCl₃) δ: 0.36-0.42 (2H, m), 0.65-0.75 (2H, m), 0.99 (9H, s), 1.03 (3H, t, J=7.4 Hz), 1.22-1.37 (1H, m),

1.45 (9H, s), 1.52-1.68 (2H, m), 1.78-1.93 (2H, m), 3.86 (2H, t, J=6.4 Hz), 3.92 (2H, d, J=6.8 Hz), 4.10 (2H, bs), 4.55 (2H, d, J=5.2 Hz), 4.63 (1H, bs), 7.04-7.10 (2H, m), 8.30-8.34 (1H, m).

- ⁵ (2) 3-(Aminomethyl)-4-butoxy-6-(cyclopropylmethoxy)-2-neopentyl-1(2H)-isoquinolinone hydrochloride
(synthesized according to the method similar to that in Example 1 (7))
Melting point 203-205°C.

¹⁰ Elemental analysis for C₂₃H₃₅N₂O₃Cl
Calculated: C, 65.31; H, 8.34; N, 6.62.
Found: C, 65.23; H, 8.25; N, 6.71.

¹⁵ ¹H-NMR(DMSO-d₆) δ:0.34-0.42 (2H, m), 0.58-0.67 (2H, m), 0.89 (9H, s), 0.99 (3H, t, J=7.3 Hz), 1.23-1.33 (1H, m), 1.52-1.63 (2H, m), 1.77-1.87 (2H, m), 3.93 (2H, t, J=6.2 Hz), 3.99 (2H, d, J=7.0 Hz), 4.03 (2H, bs), 4.23 (2H, s), 7.06 (1H, d, J=2.4 Hz), 7.19 (1H, dd, J=2.4, 9.0 Hz), 8.18 (1H, d, J=9.0 Hz), 8.50 (3H, bs).

Example 99

²⁰ 3-(Aminomethyl)-4-butoxy-2-neopentyl-6-(2-propynyloxy)-1(2H)-isoquinolinone hydrochloride
(1) Tert-butyl {4-butoxy-2-neopentyl-1-oxo-6-(2-propynyloxy)-1,2-dihydro-3-isooquinolinyl}methylcarbamate
(synthesized according to the method similar to that in

²⁵ Example 95 (1))

¹H-NMR(CDCl₃) δ:0.99 (9H, s), 1.03 (3H, t, J=7.4 Hz), 1.45 (9H, s), 1.53-1.68 (2H, m), 1.80-1.94 (2H, m), 2.57 (1H, t, J=2.2 Hz), 3.87 (2H, t, J=6.4 Hz), 4.10 (2H, bs), 4.56 (2H, d, J=4.8 Hz), 4.63 (1H, bs), 4.82 (2H, d, J=2.2 Hz), 7.11 (1H, dd, J=2.4, 8.8 Hz), 7.19 (1H, d, J=2.4 Hz), 8.35 (1H, d, J=8.8 Hz).

³⁰ (2) 3-(Aminomethyl)-4-butoxy-2-neopentyl-6-(2-propynyloxy)-1(2H)-isoquinolinone hydrochloride
(synthesized according to the method similar to that in

³⁵ Example 1 (7))

Elemental analysis for C₂₂H₃₁N₂O₃Cl 1/4H₂O

Calculated: C, 64.22; H, 7.72; N, 6.81.

Found: C, 64.36; H, 7.73; N, 6.66.

¹H-NMR(DMSO-d₆) δ:0.90 (9H, s), 1.00 (3H, t, J=7.4 Hz), 1.53-1.64 (2H, m), 1.79-1.91 (2H, m), 3.71 (1H, t, J=2.2 Hz), 3.95 (2H, t, J=6.1 Hz), 4.08 (2H, bs), 4.23 (2H, s), 5.01 (1H, d, J=2.2 Hz), 7.19-7.23 (2H, m), 8.20 (1H, d, J=9.6 Hz), 8.50 (3H, bs).

Example 100

3-(Aminomethyl)-4-butoxy-6-isobutoxy-2-neopentyl-1(2H)-

¹⁰ isoquinolinone hydrochloride

(1) Tert-butyl (4-butoxy-6-isobutoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 95

(1))

¹H-NMR(CDCl₃) δ:0.99 (9H, s), 1.04 (3H, t, J=7.2 Hz), 1.06 (6H, d, J=6.4 Hz), 1.45 (9H, s), 1.51-1.69 (2H, m), 1.79-1.93 (2H, m), 2.09-2.22 (1H, m), 3.84 (2H, d, J=6.6 Hz), 3.86 (2H, t, J=6.5 Hz), 4.10 (2H, bs), 4.56 (2H, d, J=5.6 Hz), 4.69 (1H, bs), 7.04-7.08 (2H, m), 8.31 (1H, d, J=9.4 Hz).

(2) 3-(Aminomethyl)-4-butoxy-6-isobutoxy-2-neopentyl-

1(2H)-isoquinolinone hydrochloride (synthesized

according to the method similar to that in Example 1

(7))

²⁵ Elemental analysis for C₂₃H₃₇N₂O₃Cl 1/4H₂O

Calculated: C, 64.32; H, 8.80; N, 6.52.

Found: C, 64.31; H, 8.87; N, 6.60.

¹H-NMR(DMSO-d₆) δ:0.89 (9H, s), 1.00 (3H, t, J=7.0 Hz), 1.02 (6H, d, J=6.6 Hz), 1.50-1.68 (2H, m), 1.77-1.87 (2H, m), 2.03-2.16 (1H, m), 3.92 (2H, d, J=6.6 Hz), 3.93 (2H, t, J=6.2 Hz), 4.04 (2H, bs), 4.23 (2H, s), 7.07 (1H, d, J=2.6 Hz), 7.19 (1H, dd, J=2.6, 8.8 Hz), 8.18 (1H, d, J=8.8 Hz), 8.45 (3H, bs).

Example 101

3-(Aminomethyl)-4-butoxy-6-(cyclopentyloxy)-2-neopentyl-

1(2H)-isoquinolinone hydrochloride

(1) Tert-butyl {4-butoxy-6-(cyclopentyloxy)-2-neopentyl-1-oxo-1,2-dihydro-3-isooquinolinyl}methylcarbamate
(synthesized according to the method similar to that in Example 95 (1))

⁵ ¹H-NMR(CDCl₃) δ: 0.99 (9H, s), 1.03 (3H, t, J=7.4 Hz), 1.45 (9H, s), 1.50-1.70 (4H, m), 1.73-1.98 (8H, m), 3.86 (2H, t, J=6.4 Hz), 4.10 (2H, bs), 4.55 (2H, d, J=5.2 Hz), 4.68 (1H, bs), 4.86-4.90 (1H, m), 6.98-7.04 (2H, m), 8.27-8.32 (1H, m).

¹⁰ (2) 3-(Aminomethyl)-4-butoxy-6-(cyclopentyloxy)-2-neopentyl-1(2H)-isoquinolinone hydrochloride
(synthesized according to the method similar to that in Example 1 (7))

Elemental analysis for C₂₄H₃₇N₂O₃Cl 1/4H₂O

¹⁵ Calculated: C, 65.29; H, 8.56; N, 6.34.

Found: C, 65.27; H, 8.53; N, 6.18.

¹H-NMR(DMSO-d₆) δ: 0.89 (9H, s), 1.00 (3H, t, J=7.3 Hz), 1.52-2.05 (12H, m), 3.93 (2H, t, J=6.2 Hz), 4.05 (2H, bs), 4.23 (2H, s), 4.99 (1H, bs), 7.04 (1H, d, J=2.4 Hz),
²⁰ 7.13 (1H, dd, J=2.4, 9.0 Hz), 8.16 (1H, d, J=9.0 Hz), 8.51 (3H, bs).

Example 102

3-(Aminomethyl)-4-butoxy-6-(cyclohexylmethoxy)-2-neopentyl-1(2H)-isoquinolinone hydrochloride

²⁵ (1) Tert-butyl {4-butoxy-6-(cyclohexylmethoxy)-2-neopentyl-1-oxo-1,2-dihydro-3-isooquinolinyl}methylcarbamate (synthesized according to the method similar to that in Example 95 (1))

¹H-NMR(CDCl₃) δ: 0.99 (9H, s), 1.04 (3H, t, J=7.3 Hz),

³⁰ 1.07-1.35 (3H, m), 1.45 (9H, s), 1.51-1.93 (8H, m), 3.83-3.89 (4H, m), 4.10 (2H, bs), 4.55 (2H, d, J=5.2 Hz), 4.63 (1H, bs), 7.03-7.08 (2H, m), 8.31 (1H, d, J=8.4 Hz).

(2) 3-(Aminomethyl)-4-butoxy-6-(cyclohexylmethoxy)-2-neopentyl-1(2H)-isoquinolinone hydrochloride

³⁵ (synthesized according to the method similar to that in Example 1 (7))

Elemental analysis for C₂₆H₄₁N₂O₃Cl

Calculated: C, 67.15; H, 8.89; N, 6.02.

Found: C, 67.00; H, 8.83; N, 6.03.

¹H-NMR(DMSO-d₆) δ:0.89 (9H, s), 1.00 (3H, t, J=7.3 Hz),

5 1.09-1.30 (3H, m), 1.53-1.84 (12H, m), 3.90-3.97 (4H, m),
4.08 (2H, bs), 4.23 (2H, s), 7.06 (1H, d, J=2.3 Hz),
7.18 (1H, dd, J=2.3, 8.8 Hz), 8.18 (1H, d, J=8.8 Hz),
8.47 (3H, bs).

Example 103

10 3-(Aminomethyl)-4-butoxy-6-(3,3-dimethyl-2-oxobutoxy)-2-neopentyl-1(2H)-isoquinolinone hydrochloride

(1) Tert-butyl {4-butoxy-6-(3,3-dimethyl-2-oxobutoxy)-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl}methylcarbamate (synthesized according to

15 the method similar to that in Example 95 (1))

¹H-NMR(CDCl₃) δ:0.98 (9H, s), 1.03 (3H, t, J=7.2 Hz),
1.29 (9H, s), 1.45 (9H, s), 1.51-1.65 (2H, m), 1.76-1.87
(2H, m), 3.87 (2H, t, J=6.4 Hz), 4.10 (2H, bs), 4.54 (2H,
d, J=5.2 Hz), 4.69 (1H, bs), 5.01 (2H, s), 6.98 (1H, d,
J=2.6 Hz), 7.05 (1H, dd, J=2.6, 8.8 Hz), 8.33 (1H, d,
J=8.8 Hz).

(2) 3-(Aminomethyl)-4-butoxy-6-(3,3-dimethyl-2-

oxobutoxy)-2-neopentyl-1(2H)-isoquinolinone

hydrochloride (synthesized according to the method

25 similar to that in Example 1 (7))

Elemental analysis for C₂₅H₃₉N₂O₄Cl 1/4H₂O

Calculated: C, 63.68; H, 8.44; N, 5.94.

Found: C, 63.64; H, 8.32; N, 5.99.

¹H-NMR(DMSO-d₆) δ:0.89 (9H, s), 0.98 (3H, t, J=7.2 Hz),

30 1.21 (9H, s), 1.48-1.59 (2H, m), 1.73-1.84 (2H, m), 3.90
(2H, t, J=6.5 Hz), 4.05 (2H, bs), 4.21 (2H, s), 5.39 (2H,
s), 6.90 (1H, d, J=2.5 Hz), 7.17 (1H, dd, J=2.5, 8.9 Hz),
8.18 (1H, d, J=8.9 Hz), 8.43 (3H, bs).

Example 104

35 Ethyl {{3-(aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isooquinolinyl}oxy}acetate hydrochloride

(1) Ethyl {4-butoxy-3-{{(tert-butoxycarbonyl)amino}methyl}-2-neopentyl-1-oxo-1,2-dihydro-6-isooquinolinyl}oxy}acetate (synthesized according to the method similar to that in Example 95

⁵ (1))

¹H-NMR(CDCl₃) δ: 0.98 (9H, s), 1.04 (3H, t, J=7.3 Hz), 1.30 (3H, t, J=7.1 Hz), 1.45 (9H, s), 1.52-1.67 (4H, m), 1.78-1.88 (2H, m), 3.84 (2H, t, J=6.6 Hz), 4.14 (2H, bs), 4.29 (2H, q, J=7.1 Hz), 4.55 (2H, d, J=5.2 Hz), 4.64 (1H, bs), 4.74 (2H, s), 7.02 (1H, d, J=1.5 Hz), 7.08 (1H, dd, J=1.5, 8.8 Hz), 8.33 (1H, d, J=8.8 Hz).

(2) Ethyl {{3-(aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isooquinolinyl}oxy}acetate hydrochloride (synthesized according to the method similar to that in

¹⁵ Example 1 (7))

Elemental analysis for C₂₃H₃₅N₂O₅Cl 1/2H₂O

Calculated: C, 59.54; H, 7.82; N, 6.04.

Found: C, 59.81; H, 7.70; N, 5.99.

¹H-NMR(DMSO-d₆) δ: 0.89 (9H, s), 1.00 (3H, t, J=7.1 Hz), 1.23 (3H, t, J=7.1 Hz), 1.50-1.61 (4H, m), 1.78-1.91 (2H, m), 3.91 (2H, t, J=6.2 Hz), 4.01 (2H, bs), 4.19 (2H, q, J=7.1 Hz), 4.21 (2H, s), 5.01 (2H, s), 6.99 (1H, d, J=2.6 Hz), 7.22 (1H, dd, J=2.6, 9.0 Hz), 8.20 (1H, d, J=9.0 Hz), 8.42 (3H, bs).

²⁵ Example 105

3-(Aminomethyl)-4-butoxy-6-(1-methyl-2-oxopropoxy)-2-neopentyl-1(2H)-isoquinolinone hydrochloride

(1) Tert-butyl {4-butoxy-6-(1-methyl-2-oxopropoxy)-2-neopentyl-1-oxo-1,2-dihydro-3-

³⁰ isoquinolinyl}methylcarbamate (synthesized according to the method similar to that in Example 95 (1))

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¹H-NMR(CDCl₃) δ: 0.99 (9H, s), 1.04 (3H, t, J=7.3 Hz), 1.44 (9H, s), 1.52-1.70 (5H, m), 1.78-1.92 (2H, m), 2.19 (3H, s), 3.89 (2H, t, J=6.4 Hz), 4.11 (2H, bs), 4.57 (2H, d, J=5.4 Hz), 4.73 (1H, bs), 7.08-7.17 (2H, m), 8.38 (1H,

d, J=8.8 Hz).

(2) 3-(Aminomethyl)-4-butoxy-6-(1-methyl-2-oxopropoxy)-2-neopentyl-1(2H)-isoquinolinone hydrochloride
(synthesized according to the method similar to that in

5 Example 1 (7))

Elemental analysis for C₂₃H₃₅N₂O₄Cl

Calculated: C, 62.93; H, 8.04; N, 6.38.

Found: C, 62.70; H, 8.29; N, 6.39.

¹H-NMR(DMSO-d₆) δ:0.89 (9H, s), 0.99 (3H, t, J=7.3 Hz),
10 1.48-1.60 (5H, m), 1.75-1.85 (2H, m), 2.20 (3H, s),
3.83-4.05 (4H, m), 4.21 (2H, bs), 5.15 (2H, q, J=7.0 Hz),
6.90 (1H, d, J=2.6 Hz), 7.18 (1H, dd, J=2.6, 8.8 Hz),
8.19 (1H, d, J=8.8 Hz), 8.45 (3H, bs).

Example 106

15 3-Aminomethyl-6-bromo-2-isobutyl-4-phenyl-1(2H)-isoquinolinone

(1) To a solution of 4-bromophthalic anhydride (50 g, 220 mmol) in benzene (500 mL) was added aluminum chloride (60 g, 450 mmol) by small portions under ice-cooling. The obtained mixture was stirred at room temperature for 24 h. The reaction mixture was poured into ice water and extracted with a mixed solvent of ethyl acetate - tetrahydrofuran (1/1). The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography and recrystallized from ethyl acetate - diisopropyl ether. The precipitated crystals were collected by filtration to give 2-benzoyl-4-bromobenzoic acid (33 g, 49%) as crystals.

Melting point 185-187°C.

¹H-NMR(CDCl₃) δ:7.36-7.73 (7H, m), 7.94 (1H, d, J=8.4 Hz).

(2) A mixture of 2-benzoyl-4-bromobenzoic acid (25 g, 82 mmol), potassium carbonate (12 g, 87 mmol), diethyl bromomalonate (22 g, 92 mmol), acetone (450 mL) and N,N-dimethylformamide (8 mL) was stirred at room temperature

for 15 h. The solvent was evaporated under reduced pressure. The residue was poured into water and extracted with ethyl acetate. The residue was crystallized from hexane and the crystals were collected by filtration. The obtained crystals were added to a mixture of acetic acid (235 mL) and concentrated hydrochloric acid (360 mL) and the mixture was stirred at 120°C for 8 h. The reaction mixture was cooled and concentrated. The residue was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The precipitated crystals were collected by filtration, washed with diisopropyl ether and dried to give 6-bromo-4-phenyl-1H-isochromene-3-carboxylic acid (17 g, 60%) as crystals. Melting point 205-206°C.

¹H-NMR(CDCl₃) δ:7.20-7.28 (3H, m), 7.47-7.55 (3H, m), 7.77 (1H, dd, J=8.6, 1.8 Hz), 8.26 (1H, d, J=8.6 Hz).

(3) A solution of 6-bromo-4-phenyl-1H-isochromene-3-carboxylic acid (8.0 g, 23 mmol) and isobutylamine (23 mL, 230 mmol) in methanol (120 mL) was stirred at room temperature for 15 h. The solvent was evaporated under reduced pressure, and the residue was acidified with concentrated hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. To the residue was added a solution of 4N hydrogen chloride in ethyl acetate (150 mL) and the mixture was stirred at room temperature for 3 h. The solvent was evaporated under reduced pressure, and the precipitated crystals were collected by filtration with water. The crystals were washed with water and dried to give 6-bromo-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-3-carboxylic acid (8.1 g, 87%) as crystals. Melting point 233-235°C.

¹H-NMR(CDCl₃) δ: 0.92 (6H, d, J=6.6 Hz), 2.21 (1H, m), 3.99 (2H, d, J=7.6Hz), 7.32-7.38 (3H, m), 7.42-7.47 (3H, m), 7.60 (1H, dd, J=8.4, 2.0Hz), 8.26 (1H, d, J=8.4Hz).

(4) 6-Bromo-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-3-

5 carboxylic acid (12.3 g, 30.7 mmol) was dissolved in tetrahydrofuran (100 mL), and oxalyl chloride (3.2 mL, 36.8 mmol) and N,N-dimethylformamide (5 drops) were added thereto. The mixture was stirred at room temperature for 1 h. The reaction mixture was

10 concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (50 mL). The obtained solution was added dropwise to a suspension of sodium tetrahydroborate (4.0 g, 107 mmol) in 1,2-dimethoxyethane (50 mL) at 0°C. The obtained mixture was

15 stirred at 0°C for 1 h. The reaction mixture was poured into 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from

20 diethyl ether - n-hexane to give 6-bromo-3-hydroxymethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (10.7 g; 90%) as crystals.

Melting point 176-177°C.

¹H-NMR(CDCl₃) δ: 0.97 (6H, d, J=6.6Hz), 2.22 (1H, m), 2.35 (1H, t, J=5.8Hz), 4.21 (2H, d, J=7.6Hz), 4.44 (2H, d, J=5.8Hz), 7.10 (1H, d, J=1.8Hz), 7.30-7.35 (2H, m), 7.47 (1H, dd, J=8.4, 1.8Hz), 7.50-7.56 (3H, m), 8.20 (1H, d, J=8.4Hz).

(5) To a solution of 6-bromo-3-hydroxymethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (8.7 g, 22.5 mmol) and pyridine (5 drops) in tetrahydrofuran (30 mL) and toluene (30 mL) was added thionyl chloride (3.4 mL, 47.3 mmol). The obtained mixture was stirred at room temperature for 3 h. The reaction mixture was

30 concentrated, poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over

35

anhydrous magnesium sulfate and concentrated under reduced pressure to give 6-bromo-3-chloromethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (8.2 g, 90%) as crystals.

⁵ Melting point 145-146°C.

¹H-NMR(CDCl₃) δ: 1.01 (6H, d, J=6.6Hz), 2.22 (1H, m), 4.17 (2H, d, J=7.6Hz), 4.37(2H, s), 7.14 (1H, d, J=1.8Hz), 7.31-7.37 (2H, m), 7.49-7.55 (3H, m), 7.59 (1H, dd, J=8.4, 1.8Hz), 8.34 (1H, d, J=8.4Hz).

¹⁰ (7) A solution of 6-bromo-3-chloromethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (10 g, 24.7 mmol) in tetrahydrofuran (20 mL) and a solution of 2M ammonia in ethanol (200 mL) were sealed in a stainless tube and stirred at 140°C for 5 h. The reaction mixture was

¹⁵ cooled and concentrated. The residue was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was crystallized from diethyl ether and the

²⁰ precipitated crystals were collected by filtration to give 3-aminomethyl-6-bromo-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (5.6 g, 53%) as crystals.

Melting point 129-130°C

¹H NMR (CDCl₃) δ: 1.00 (6H, d, J = 6.6 Hz), 1.33 (2H, br), 2.12-2.38 (1H, m), 3.65 (2H, s), 4.20 (2H, d, J = 7.8 Hz), 7.08 (1H, d, J = 1.6 Hz), 7.21-7.35 (2H, m), 7.42-7.60 (4H, m), 8.32 (1H, d, J = 9.0 Hz).

Elemental analysis for C₂₀H₂₁BrN₂O

Calculated:C, 62.35; H, 5.49; N, 7.27.

³⁰ Found: C, 62.36; H, 5.64; N, 7.44.

Example 107

Methyl 3-aminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxylate hydrochloride

(1) To a solution of 3-aminomethyl-6-bromo-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 106 (7)) (5.6 g,

14.5 mmol) and 4-dimethylaminopyridine (20 mg) in tetrahydrofuran (50 mL) was added di-t-butyl dicarbonate (6.3 g, 2.9 mmol). The obtained mixture was stirred at room temperature for 1 h. The reaction mixture was
5 poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was crystallized from diethyl ether to give 3-tert-butoxycarbonylaminomethyl-6-bromo-
10 2-isobutyl-4-phenyl-1(2H)-isoquinolinone (6.6 g, 94%) as crystals.

¹H-NMR(CDCl₃) δ: 1.00 (6H, d, J=7.0 Hz), 1.43 (9H, s), 2.23 (1H, m), 4.06 (2H, d, J=7.8 Hz), 4.19 (2H, d, J=5.4 Hz), 4.50 (1H, bs), 7.08 (1H, d, J=2.0Hz), 7.21-7.25 (2H, m), 7.48-7.56 (4H, m), 8.30 (1H, d, J=8.8Hz).

(2) A mixture of 3-tert-butoxycarbonylaminomethyl-6-bromo-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (3.0 g, 6.2 mmol), 1,3-bis(diphenylphosphino)propane (0.45 g, 1.1 mmol) and triethylamine (0.69 g, 6.8 mmol) in
20 dimethyl sulfoxide (30 ml) and methanol (15 ml) was stirred under a carbon monoxide atmosphere at room temperature for 30 min. Palladium acetate (0.25 g, 1.1 mmol) was added to the resulting mixture and the mixture was stirred under a carbon monoxide atmosphere with
25 heating at 80°C for 15 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by
30 silica gel column chromatography to give methyl 3-tert-butoxycarbonylaminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxylate (1.92 g, 83.5%) as crystals.
Melting point 205-206°C.

Elemental analysis for C₂₇H₃₂N₂O₅
35 Calculated: C, 69.81; H, 6.94; N, 6.03.
Found: C, 69.71; H, 6.80; N, 6.13.

¹H-NMR(CDCl₃) δ: 1.01 (6H, d, J=6.6 Hz), 1.43 (9H, s), 2.26 (1H, m), 3.85 (3H, s), 4.09 (2H, d, J=7.6 Hz), 4.22 (2H, d, J=5.6 Hz), 4.47 (1H, bs), 7.23-7.28 (2H, m), 7.49-7.56 (3H, m), 7.66 (1H, d, J=1.0Hz), 8.05 (1H, dd, ⁵J=1.7, 8.0 Hz), 8.52 (1H, d, J=8.0 Hz).

- (3) To a solution of methyl 3-tert-butoxycarbonylaminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxylate (0.2 g, 0.43 mmol) in tetrahydrofuran (10 mL) was added a solution of 10% hydrogen chloride in methanol (20 mL). The obtained solution was stirred at room temperature for 15 h. The reaction mixture was concentrated under reduced pressure and the residue was crystallized from diethyl ether to give methyl 3-aminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxylate hydrochloride (0.17 g, 99%) as crystals.

Elemental analysis for C₂₂H₂₄N₂O₃ HCl 1/4H₂O

Calculated: C, 65.18; H, 6.34; N, 6.91.

Found: C, 65.08; H, 6.29; N, 6.86.

- (2) ¹H-NMR(DMSO-d₆) δ: 0.93 (6H, d, J=6.6 Hz), 2.12 (1H, m), 3.80 (3H, s), 3.89 (2H, s), 4.10 (2H, d, J=6.6 Hz), 7.42-7.46 (2H, m), 7.54 (1H, d, J=1.6 Hz), 7.54-7.62 (3H, m), 8.07 (1H, dd, J=8.4 Hz), 8.47 (1H, d, J=8.4 Hz), 8.58 (3H, s).

25 Example 108

- 3-Aminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxylic acid hydrochloride
(1) To a solution of methyl 3-tert-butoxycarbonylaminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxylate (synthesized according to the method similar to that in Example 107 (2)) (0.28 g, 0.6 mmol) in tetrahydrofuran (10 ml) and methanol (10 ml) was added 1N sodium hydroxide (5 ml). The obtained mixture was stirred at room temperature for 2 h. The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate.

The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diethyl ether to give 3-tert-

⁵ butoxycarbonylaminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxylic acid (1.54 g, 98.7%) as crystals.

Elemental analysis for C₂₆H₃₀N₂O₅

Calculated: C, 69.31; H, 6.71; N, 6.22.

¹⁰ Found: C, 69.17; H, 6.59; N, 6.27.

¹H-NMR(CDCl₃) δ: 0.96 (6H, d, J=6.6 Hz), 1.07 (3H, t, J=7.4 Hz), 1.49 (9H, s), 1.50-1.72 (2H, m), 1.84-1.98 (2H, m), 2.14-2.21 (1H, m), 3.90 (2H, t, J=6.4 Hz), 4.00 (2H, d, J=6.8 Hz), 4.55 (2H, d, J=5.0 Hz), 5.37 (1H, bs), 8.08-8.13 (1H, m), 8.35-8.46 (2H, m).

(2) To a solution of 3-tert-butoxycarbonylaminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxylic acid (0.15 g, 0.33 mmol) in tetrahydrofuran (6 mL) was added a solution of 4N hydrogen chloride in dioxane (10 mL).

²⁰ The obtained solution was stirred at room temperature for 15 h. The reaction mixture was concentrated under reduced pressure, and the residue was crystallized from diethyl ether to give 3-aminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxylic acid hydrochloride (0.09 g, 69%) as crystals.

¹H-NMR(DMSO-d₆) δ: 0.89 (6H, d, J=6.6 Hz), 1.01 (3H, t, J=7.4 Hz), 1.50-1.69 (2H, m), 1.80-1.93 (2H, m), 1.99-2.12 (1H, m), 3.97 (2H, t, J=6.4 Hz), 3.99 (2H, d, J=7.6 Hz), 4.21 (2H, s), 8.09 (1H, dd, J=1.4, 8.4 Hz), 8.34 (1H, d, J=1.4 Hz); 8.38 (1H, d, J=8.4 Hz), 8.69 (3H, bs).

Example 109

3-Aminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxamide hydrochloride [3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-

³⁵ isoquinolinecarboxamide hydrochloride]

(1) A solution of 3-tert-butoxycarbonylaminomethyl-2-

isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxylic acid (synthesized according to the method similar to that in Example 108 (1)) (0.6 g, 1.3 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.5 g, 5 2.6 mmol) and 1-hydroxybenzotriazole ammonium salt (0.4 g, 2.6 mmol) in N,N-dimethylformamide (3 ml) was stirred at room temperature for 3 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed successively with saturated aqueous 10 sodium hydrogencarbonate solution and brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was crystallized from diethyl ether - n-hexane to give 3-tert-butoxycarbonylaminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxamide (0.5 g, 86%) as crystals.

¹H-NMR(CDCl₃) δ: 1.00 (6H, d, J=6.6 Hz), 1.43 (9H, s), 2.24 (1H, m), 4.08 (2H, d, J=7.2Hz), 4.20 (2H, d, J=5.4Hz), 4.68 (1H, bs), 5.73 (1H, bs), 6.08 (1H, bs); 7.24-7.29 (2H, m), 7.38 (1H, d, J=2.0Hz), 7.47-7.56 (3H, m), 7.74 (1H, dd, J=8.8, 2.0Hz), 8.45 (1H, d, J=8.8Hz).

(2) To a solution of 3-tert-butoxycarbonylaminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxamide (0.15 g, 0.33 mmol) in tetrahydrofuran (6 mL) was added a solution of 4N hydrogen chloride in dioxane (10 mL). 20

The obtained solution was stirred at room temperature for 6 h. The reaction mixture was concentrated under reduced pressure, and the residue was crystallized from diethyl ether to give 3-aminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxamide hydrochloride (0.11 g, 25 85%) as crystals.

Melting point 240-242°C.

¹H-NMR(DMSO-d₆) δ: 0.92 (6H, d, J=6.6Hz), 2.11 (1H, m), 3.87 (2H, d, J=5.6Hz), 4.10 (2H, d, J=7.2Hz), 7.39 (1H, d, 1.4Hz), 7.40-7.43 (2H, m), 7.56-7.62 (4H, m), 8.00 (35 1H, dd, J=8.4, 1.4Hz), 8.16 (1H, s), 8.37 (1H, d, J=8.4Hz), 8.61 (3H, bs).

Example 110

3-Aminomethyl-6-benzyloxycarbonylamino-2-isobutyl-4-phenyl-1(2H)-isoquinolinone hydrochloride

(1) A solution of 3-tert-butoxycarbonylaminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxylic acid (synthesized according to the method similar to that in Example 108 (1)) (0.5 g, 1.1 mmol), diphenylphosphoryl azide (0.28 ml, 1.3 mmol) and triethylamine (0.18 ml, 1.3 mmol) in N,N-dimethylformamide (5 ml) was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in toluene (20 ml) and the mixture was stirred with heating at 100°C for 2 h. To the obtained mixture was added benzyl alcohol (0.14 ml, 1.3 mmol) and the mixture was stirred with heating at 100°C for 1 h. The reaction mixture was cooled, poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was crystallized from diisopropyl ether to give 6-benzyloxycarbonylamino-3-tert-butoxycarbonylaminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (0.47 g, 77%) as crystals.

¹H-NMR(CDCl₃) δ: 0.99 (6H, d, J=6.6 Hz), 1.42 (9H, s), 2.23 (1H, m), 4.05 (2H, d, J=7.6Hz), 4.18 (2H, d, J=5.2 Hz), 4.47 (1H, bs), 5.13 (2H, s), 6.75 (1H, d, J=1.8Hz), 6.76 (1H, s), 7.21-7.26 (2H, m), 7.34-7.75 (5H, m), 7.45-7.56 (3H, m), 7.65 (1H, dd, J=8.8, 1.8Hz), 8.41 (1H, d, J=8.8Hz).

(2) To a solution of 6-benzyloxycarbonylamino-3-tert-butoxycarbonylaminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (0.07 g, 0.13 mmol) in tetrahydrofuran (2 mL) was added a solution of 4N hydrogen chloride in ethyl acetate (10 mL). The obtained solution was

stirred at room temperature for 5 h. The reaction mixture was concentrated under reduced pressure and the residue was crystallized from diethyl ether to give 3-aminomethyl-6-benzyloxycarbonylamino-2-isobutyl-4-

- 5 phenyl-1(2H)-isoquinolinone hydrochloride (0.05 g, 81%) as crystals.

¹H-NMR(DMSO-d₆) δ:0.91 (6H, d, J=6.6 Hz), 2.08 (1H, m), 3.84 (2H, s), 4.03 (2H, d, J=7.4 Hz), 5.08 (2H, s), 7.22 (1H, d, J=1.8 Hz), 7.35-7.37 (7H, s), 7.54-7.58 (2H, m),

- 10 7.64 (1H, dd, J=8.8, 1.8Hz), 8.24 (1H, d, J=8.8 Hz), 8.44 (3H, s), 10.16 (1H, s).

Example 111

6-Amino-3-aminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone dihydrochloride

- 15 (1) To a mixed solution of 6-benzyloxycarbonylamino-3-tert-butoxycarbonylaminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 110.(1)) (0.45 g, 0.81 mmol) in tetrahydrofuran (20 ml) and ethanol (20 ml) was added 5% palladium-carbon (0.1 g). The obtained mixture was hydrogenated at ambient temperature and atmospheric pressure. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The precipitated crystals were collected by filtration to give 6-amino-3-tert-butoxycarbonylaminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (0.31 g, 87.0%) as crystals.

¹H-NMR(CDCl₃) δ:0.99 (6H, d, J=6.8 Hz), 1.42 (9H, s), 2.22 (1H, m), 3.94 (2H, bs), 4.02 (2H, d, J=7.4Hz), 4.15 (2H, d, J=5.4Hz), 4.40 (1H, bs), 6.12 (1H, d, J=2.2Hz), 6.78 (1H, dd, J=8.8, 2, 2Hz), 7.21-7.26 (2H, m), 7.44-7.53 (3H, m), 8.27 (1H, d, J=8.8Hz).

- 30 (2) 6-Amino-3-aminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone dihydrochloride was synthesized from 6-amino-3-tert-butoxycarbonylaminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone according to the method

similar to that in Example 110 (2).

¹H-NMR(DMSO-d₆) δ:0.90 (6H, d, J=6.6 Hz), 2.05 (1H, m), 3.76 (2H, bs), 3.99 (2H, d, J=6.6Hz), 5.44 (3H, bs), 6.00 (1H, d, J=2.0Hz), 6.84 (1H, dd, t, J=8.8, 2.0Hz),
5 7.34-7.38 (2H, m), 7.50-7.59 (3H, m), 8.03 (1H, d, J=8.8 Hz), 8.48 (3H, bs).

Example 112

6-Acetylamino-3-aminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone hydrochloride

10 (1) A mixture of 6-amino-3-tert-butoxycarbonylaminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 111 (1)) (0.1 g, 0.24 mmol), acetyl chloride (38 mg, 0.48 mmol), sodium
15 hydrogencarbonate (81 mg, 0.96 mmol), water (0.5 ml) and ethyl acetate (5 ml) was stirred at room temperature for 2 h. The reaction mixture was extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under
20 reduced pressure. The residue was crystallized from diisopropyl ether to give 6-acetylamino-3-tert-butoxycarbonylaminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (80 mg, 73%) as crystals.

¹H-NMR(CDCl₃) δ:0.87 (6H, d, J=7.0 Hz), 1.42 (9H, s),
25 2.10 (3H, s), 2.23 (1H, m), 4.05 (2H, d, J=7.4Hz), 4.19 (2H, d, J=5.6Hz), 4.60 (1H, bs), 6.95 (1H, s), 7.24-7.28 (2H, m), 7.37 (1H, s), 7.47-7.55 (3H, m), 7.69 (1H, d, J=8.8Hz), 8.37 (1H, d, J=8.8Hz).

(2) 6-Acetylamino-3-aminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone hydrochloride was synthesized from 6-acetylamino-3-tert-butoxycarbonylaminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone according to the method similar to that in Example 110 (2).

¹H-NMR(DMSO-d₆) δ:0.91 (6H, d, J=6.6 Hz), 1.98 (3H, s),
35 2.08 (1H, m), 3.84 (2H, s), 4.03 (2H, d, J=7.0Hz), 7.19 (1H, d, J=1.8Hz), 7.35-7.39 (2H, m), 7.49-7.58 (3H, m),

7.86 (1H, dd, J=8.8, 1.8Hz), 8.25 (1H, d, J=8.8Hz), 8.45 (3H, bs), 10.28 (1H, s).

The compounds of the following Examples 113 to 130 were synthesized according to the method similar to that
5 in Example 106.

Example 113

3-(Aminomethyl)-6-chloro-2-ethyl-4-phenyl-1(2H)-isoquinolinone

Melting point 126-127°C

10 $^1\text{H-NMR}$ (CDCl_3) δ : 1.39 (2H, br), 1.42 (3H, t, J = 7.0 Hz), 3.64 (2H, s), 4.43 (2H, q, J = 7.0 Hz), 6.91 (1H, d, J = 2.2 Hz), 7.23-7.31 (2H, m), 7.38 (1H, dd, J = 2.2 and 8.4 Hz), 7.45-7.57 (3H, m), 8.41 (1H, d, J = 8.4 Hz).
Elemental analysis for $\text{C}_{18}\text{H}_{17}\text{ClN}_2\text{O} \cdot 0.125\text{H}_2\text{O}$

15 Calculated:C, 68.62; H, 5.51; N, 8.89.

Found: C, 68.61; H, 5.40; N, 8.84.

Example 114

3-(Aminomethyl)-6-chloro-4-phenyl-2-propyl-1(2H)-isoquinolinone

20 $^1\text{H-NMR}$ (CDCl_3) δ : 1.04 (3H, t, J = 7.4 Hz), 1.17 (2H, br), 1.71-1.93 (2H, m), 3.63 (2H, s), 4.28 (2H, t, J = 7.6 Hz), 6.90 (1H, d, J = 2.2 Hz), 7.21-7.32 (2H, m), 7.37 (1H, dd, J = 2.2 and 8.4 Hz), 7.41-7.58 (3H, m), 8.40 (1H, d, J = 8.4 Hz).

25 Elemental analysis for $\text{C}_{19}\text{H}_{19}\text{ClN}_2\text{O}$

Calculated:C, 69.83; H, 5.86; N, 8.57.

Found: C, 69.97; H, 5.90; N, 8.49.

Example 115

3-(Aminomethyl)-2-butyl-6-chloro-4-phenyl-1(2H)-isoquinolinone

20 $^1\text{H-NMR}$ (CDCl_3) δ : 1.00 (3H, t, J = 7.4 Hz), 1.23 (2H, br), 1.38-1.60 (2H, m), 1.68-1.84 (2H, m), 3.63 (2H, s), 4.33 (2H, t, J = 7.6 Hz), 6.90 (1H, d, J = 2.0 Hz), 7.22-7.31 (2H, m), 7.38 (1H, dd, J = 2.0 and 8.8 Hz), 7.45-7.58 (3H, m), 8.41 (1H, d, J = 8.8 Hz).

35 Elemental analysis for $\text{C}_{20}\text{H}_{21}\text{ClN}_2\text{O}$

Calculated:C, 70.48; H, 6.21; N, 8.22.

Found: C, 70.27; H, 6.18; N, 8.09.

Example 116

3-(Aminomethyl)-6-bromo-2-methyl-4-phenyl-1(2H)-
5 isoquinolinone

¹H-NMR (CDCl₃) δ: 1.30 (2H, br), 3.66 (2H, s), 3.84 (3H,
s), 7.10 (1H, d, J = 2.0 Hz), 7.20-7.32 (2H, m), 7.45-
7.59 (4H, m), 8.33 (1H, d, J = 8.8 Hz).

Elemental analysis for C₁₇H₁₅BrN₂O

10 Calculated:C, 59.49; H, 4.41; N, 8.16.

Found: C, 59.61; H, 4.65; N, 7.78.

Example 117

3-(Aminomethyl)-6-chloro-2-pentyl-4-phenyl-1(2H)-
isoquinolinone

15 ¹H-NMR (CDCl₃) δ: 0.93 (3H, t, J = 7.4 Hz), 1.20-1.53 (6H,
m), 1.70-1.90 (2H, m), 3.63 (2H, s), 4.31 (2H, t, J =
8.0 Hz), 6.90 (1H, d, J = 2.2 Hz), 7.22-7.31 (2H, m);
7.37 (1H, dd, J = 2.2 and 8.4 Hz), 7.45-7.58 (3H, m),
8.40 (1H, d, J = 8.4 Hz).

20 Elemental analysis for C₂₁H₂₃ClN₂O

Calculated:C, 71.07; H, 6.53; N, 7.89.

Found: C, 70.82; H, 6.34; N, 7.72.

Example 118

3-(Aminomethyl)-6-chloro-2-isobutyl-4-phenyl-1(2H)-
25 isoquinolinone

Melting point 123-124°C

¹H-NMR (CDCl₃) δ: 1.00 (6H, d, J = 6.6 Hz), 1.18 (2H, br),
2.12-2.38 (1H, m), 3.66 (2H, s), 4.20 (2H, d, J = 7.4
Hz), 6.90 (1H, d, J = 1.6 Hz), 7.21-7.31 (2H, m), 7.37
30 (1H, dd, J = 1.6 and 8.4 Hz), 7.45-7.58 (3H, m), 8.40
(1H, d, J = 8.4 Hz).

Elemental analysis for C₂₀H₂₁ClN₂O

Calculated:C, 70.48; H, 6.21; N, 8.22.

Found: C, 70.35; H, 6.07; N, 8.10.

Example 119

3-(Aminomethyl)-6-chloro-2-(cyclohexylmethyl)-4-phenyl-

1(2H)-isoquinolinone

¹H-NMR (CDCl₃) δ: 1.00-1.47 (8H, m), 1.56-2.00 (5H, m), 3.66 (2H, s), 4.21 (2H, d, J = 6.8 Hz), 6.90 (1H, d, J = 2.0 Hz), 7.22-7.32 (2H, m), 7.37 (1H, dd, J = 2.0 and 8.8 Hz), 7.47-7.58 (3H, m), 8.40 (1H, d, J = 8.8 Hz).

Elemental analysis for C₂₃H₂₅ClN₂O

Calculated: C, 72.52; H, 6.62; N, 7.35.

Found: C, 72.34; H, 6.76; N, 7.21.

Example 120

- ¹⁰ 3-(Aminomethyl)-6,7-dichloro-4-(4-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone hydrochloride

¹H-NMR (CDCl₃, free base) δ: 0.99 (6H, d, J = 6.8 Hz), 1.36 (2H, br), 2.10-2.35 (1H, m), 3.65 (2H, s), 4.20 (2H, d, J = 7.6 Hz), 6.99 (1H, s), 7.24 (4H, d, J = 7.4 Hz),

- ¹⁵ 8.53 (1H, s).

Elemental analysis for C₂₀H₁₉Cl₂N₂OF·HCl·H₂O.

Calculated: C, 53.65; H, 4.95; N, 6.26.

Found: C, 53.69; H, 4.84; N, 5.96.

Example 121

- ²⁰ 3-(Aminomethyl)-6,7-dichloro-2-isobutyl-4-phenyl-1(2H)-isoquinolinone

¹H-NMR (CDCl₃) δ: 1.00 (6H, d, J = 7.0 Hz), 1.13 (2H, br), 2.10-2.36 (1H, m), 3.65 (2H, s), 4.20 (2H, d, J = 7.4 Hz), 7.02 (1H, s), 7.20-7.32 (2H, m), 7.45-7.59 (3H, m),

- ²⁵ 8.54 (1H, s).

Elemental analysis for C₂₀H₂₀Cl₂N₂O

Calculated: C, 64.01; H, 5.37; N, 7.46.

Found: C, 63.71; H, 5.39; N, 7.23.

Example 122

- ³⁰ 3-(Aminomethyl)-6-chloro-2-neopentyl-4-phenyl-1(2H)-isoquinolinone

Melting point 173-174°C

¹H-NMR (CDCl₃) δ: 1.02 (9H, s), 1.23 (2H, br), 3.71 (2H, s), 4.30 (2H, br), 6.90 (1H, d, J = 2.2 Hz), 7.20-7.30

- ³⁵ (2H, m), 7.37 (1H, dd, J = 2.2 and 8.4 Hz), 7.42-7.68 (3H, m), 8.39 (1H, d, J = 8.4 Hz).

Elemental analysis for C₂₁H₂₃ClN₂O

Calculated:C, 71.07; H, 6.53; N, 7.89.

Found: C, 70.89; H, 6.54; N, 7.61.

Example 123

5 3-(Aminomethyl)-2-isobutyl-4-phenyl-1(2H)-isoquinolinone

Melting point 129-130°C

¹H-NMR (CDCl₃) δ: 1.01 (6H, d, J = 7.0 Hz), 1.23 (2H, br), 2.17-2.40 (1H, m), 3.68 (2H, s), 4.22 (2H, d, J = 7.8 Hz), 6.90-7.00 (1H, m), 7.23-7.34 (2H, m), 7.38-7.57 (5H, m), 8.44-8.52 (1H, m).

Elemental analysis for C₂₀H₂₂N₂O

Calculated:C, 78.40; H, 7.24; N, 9.14.

Found: C, 78.30; H, 7.50; N, 9.06.

Example 124

15 3-(Aminomethyl)-4-(4-chlorophenyl)-2-isobutyl-1(2H)-isoquinolinone

Melting point 119-120°C

¹H-NMR (CDCl₃) δ: 1.00 (6H, d, J = 6.6 Hz), 1.15 (1H, br), 1.61 (1H, br), 2.14-2.39 (1H, m), 3.67 (2H, s), 4.21 (2H, d, J = 7.8 Hz), 6.88-6.97 (1H, m), 7.20-7.29 (2H, m), 7.40-7.56 (4H, m), 8.43-8.52 (1H, m).

Elemental analysis for C₂₆H₂₁ClN₂O

Calculated:C, 70.48; H, 6.21; N, 8.22.

Found: C, 70.36; H, 6.40; N, 8.19.

25 **Example 125**

3-(Aminomethyl)-4-(4-methylphenyl)-2-isobutyl-1(2H)-isoquinolinone hydrochloride

Melting point 178-180°C (dec.)

¹H-NMR (CDCl₃, free base) δ: 1.00 (6H, d, J = 6.6 Hz), 1.48 (2H, br), 2.18-2.37 (1H, m), 2.46 (3H, s), 3.69 (2H, s), 4.22 (2H, d, J = 7.8 Hz), 6.95-7.04 (1H, m), 7.17 (2H, d, J = 8.0 Hz), 7.31 (2H, d, J = 7.0 Hz), 7.37-7.53 (2H, m), 8.43-8.53 (1H, m).

Elemental analysis for C₂₁H₂₄N₂O·HCl·0.5H₂O

35 Calculated:C, 68.93; H, 7.16; N, 7.66.

Found: C, 69.25; H, 7.11; N, 7.30.

Example 126

3-(Aminomethyl)-6-fluoro-2-isobutyl-4-phenyl-1(2H)-isoquinolinone

¹H-NMR (CDCl₃) δ: 1.00 (6H, d, J = 6.6 Hz), 1.12 (2H, br), 2.15-2.38 (1H, m), 3.67 (2H, s), 4.20 (2H, d, J = 7.4 Hz), 6.56 (1H, dd, J = 2.6 and 10.6 Hz), 7.13 (1H, dt, J = 2.6 and 8.8 Hz), 7.23-7.33 (2H, m), 7.41-7.57 (3H, m), 8.48 (1H, dd, J = 5.8 and 8.8 Hz).

Elemental analysis for C₂₀H₂₁FN₂O·0.25H₂O

¹⁰ Calculated:C, 73.04; H, 6.59; N, 8.52.

Found: C, 73.32; H, 6.72; N, 8.43.

Example 127

3-(Aminomethyl)-2-isobutyl-6-methoxy-4-phenyl-1(2H)-isoquinolinone

¹⁵ ¹H-NMR (CDCl₃) δ: 1.00 (6H, d, J = 6.6 Hz), 1.26 (2H, br), 2.15-2.38 (1H, m), 3.65 (2H, s), 3.67 (3H, s), 4.18 (2H, d, J = 7.2 Hz), 6.30 (1H, d, J = 2.4 Hz), 7.02 (1H, dd, J = 2.4 and 8.8 Hz), 7.23-7.34 (2H, m), 7.39-7.57 (3H, m), 8.41 (1H, d, J = 8.8 Hz).

²⁰ Elemental analysis for C₂₁H₂₄N₂O₂

Calculated:C, 74.97; H, 7.19; N, 8.33.

Found: C, 74.73; H, 7.40; N, 8.32.

Example 128

3-(Aminomethyl)-6-ethoxy-2-isobutyl-4-phenyl-1(2H)-isoquinolinone

¹H-NMR (CDCl₃) δ: 1.00 (6H, d, J = 7.0 Hz), 1.21 (2H, br), 1.33 (3H, t, J = 7.0 Hz), 2.13-2.38 (1H, m), 3.65 (2H, s), 3.88 (2H, q, J = 7.0 Hz), 4.18 (2H, d, J = 7.4 Hz), 6.29 (1H, d, J = 2.6 Hz), 7.01 (1H, dd, J = 2.6 and 8.8 Hz), 7.22-7.32 (2H, m), 7.41-7.55 (3H, m), 8.39 (1H, d, J = 8.8 Hz).

Elemental analysis for C₂₂H₂₆N₂O₂

Calculated:C, 75.40; H, 7.48; N, 7.99.

Found: C, 75.43; H, 7.69; N, 8.17.

Example 129

3-(Aminomethyl)-2-isobutyl-4-phenyl-6-propoxy-1(2H)-

isoquinolinone

¹H-NMR (CDCl₃) δ: 0.95 (3H, t, J = 7.4Hz), 0.99 (6H, d, J = 7.0 Hz), 1.32 (2H, br), 1.61-1.82 (2H, m), 2.13-2.38 (1H, m), 3.64 (2H, s), 3.77 (2H, t, J = 6.6Hz), 4.18 (2H, d, J = 7.4 Hz), 6.28 (1H, d, J = 2.6 Hz), 7.01 (1H, dd, J = 2.6 and 9.2 Hz), 7.22-7.31 (2H, m), 7.42-7.56 (3H, m), 8.39 (1H, d, J = 9.2 Hz).

Elemental analysis for C₂₃H₂₈N₂O₂

Calculated:C, 75.79; H, 7.74; N, 7.69.

¹⁰ Found: C, 75.81; H, 7.45; N, 7.56.

Example 130**3-(Aminomethyl)-2-isobutyl-6,7-dimethoxy-4-phenyl-1(2H)-isoquinolinone**

¹H-NMR (CDCl₃) δ: 1.01 (6H, d, J = 6.6 Hz), 1.34 (2H, br), 2.15-2.40 (1H, m), 3.66 (5H, s), 4.01 (3H, s), 4.21 (2H, d, J = 7.4 Hz), 6.28 (1H, s), 7.25-7.35 (2H, m), 7.40-7.57 (3H, m), 7.87 (1H, s).

Elemental analysis for C₂₂H₂₆N₂O₃·0.5H₂O

Calculated:C, 70.38; H, 7.25; N, 7.46.

²⁰ Found: C, 70.56; H, 7.36; N, 7.39.

Example 131**3-(Aminomethyl)-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carbonitrile hydrochloride**

(1) A solution of 3-tert-butoxycarbonylaminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxamide (synthesized according to the method similar to that in Example 109 (1)) (0.3 g, 0.67 mmol) and cyanuric chloride (0.37 g, 2 mmol) in N,N-dimethylformamide (3 mL) was stirred at 0°C for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed successively with water, 10% aqueous citric acid solution, saturated aqueous sodium hydrogencarbonate solution and brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give a amorphous solid of

tert-butyl (6-cyano-2-isobutyl-4-phenyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.28 g, 97%).

¹H-NMR(CDCl₃) δ: 1.01 (6H, d, J=7.0 Hz), 1.43 (9H, s), 2.24 (1H, m), 4.09 (2H, d, J=7.0 Hz), 4.23 (2H, d, J=5.4 Hz), 4.43 (1H, bs), 7.21~7.29 (3H, m), 7.51~7.59 (3H, m), 7.65 (1H, dd, J=1.4, 8.0 Hz), 8.55 (1H, d, J=8.0 Hz).

(2) 3-(Aminomethyl)-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carbonitrile hydrochloride was synthesized from tert-butyl (6-cyano-2-isobutyl-4-

10 phenyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate in the same manner as in Example 1 (7).

¹H-NMR(DMSO-d₆) δ: 0.93 (6H, d, J=6.6 Hz), 2.11 (1H, m), 3.89 (2H, s), 4.11 (2H, d, J=7.4Hz), 7.22 (1H, d, J=1.6Hz), 7.42~7.46 (2H, m), 7.58~7.61 (3H, m), 7.97 (1H,

15 dd, J=1.6, 8.4Hz), 8.48 (1H, d, J=8.4 Hz), 8.67 (3H, bs).

Example 132

3-(Aminomethyl)-4-phenyl-6-(1-pyrrolidinylcarbonyl)-2-isobutyl-1(2H)-isoquinolinone hydrochloride

(1) A mixture of 3-tert-butoxycarbonylaminomethyl-2-

20 isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxylic acid (synthesized according to the method similar to that in Example 108 (1)) (100 mg, 0.22 mmol), hydrochloric acid 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (63 mg, 0.33 mmol), 1-hydroxy-7-

25 azabenzotriazole (30 mg, 0.22 mmol), pyrrolidine (31 mg, 0.44 mmol) and N,N-dimethylformamide (3 mL) was stirred at room temperature for 3 h. The reaction mixture was poured into 10% aqueous citric acid solution and extracted with ethyl acetate. The extract was dried

30 over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 3-(tert-butoxycarbonylaminomethyl)-2-isobutyl-4-phenyl-6-(1-pyrrolidinylcarbonyl)-1(2H)-isoquinolinone (70 mg, 64%)

35 as an amorphous solid.

¹H-NMR(CDCl₃) δ: 1.01 (6H, d, J=6.6 Hz), 1.43 (9H, s),

1.79-1.99 (4H, m), 2.25 (1H, m), 3.21 (2H, t, J=6.2 Hz),
 3.57 (2H, t, J=6.8Hz), 4.09 (2H, d, J=7.6 Hz), 4.21 (2H,
 d, J=6.0Hz), 4.44 (1H, bs), 7.08 (1H, d, J=1.6Hz), 7.21-
 7.27 (2H, m), 7.45-7.51 (3H, m), 7.56 (1H, dd, J=8.4,
 5 1.6Hz), 8.50 (1H, d, J=8.4Hz).

(2) 3-(Aminomethyl)-2-isobutyl-4-phenyl-6-(1-pyrrolidinylcarbonyl)-1(2H)-isoquinolinone hydrochloride was synthesized from 3-(tert-butoxycarbonylaminomethyl)-2-isobutyl-4-phenyl-6-(1-pyrrolidinylcarbonyl)-1(2H)-isoquinolinone in the same manner as in Example 1 (7).
¹H-NMR(DMSO-d₆) δ: 0.93 (6H, d, J=6.6 Hz), 1.70-1.90 (4H, m), 2.11 (1H, m), 3.20 (2H, t, J=6.4Hz), 3.90 (2H, t, J=6.2Hz), 3.88 (2H, s), 4.09 (2H, d, J=7.4Hz), 6.96 (1H, d, J=1.6Hz), 7.39-7.44 (2H, m), 7.56-7.64 (3H, m), 7.69 (1H, dd, J=8.4, 1.6Hz), 8.37 (1H, d, J=8.4Hz), 8.55 (3H, bs).

The compounds of the following Examples 133 to 141 were synthesized according to the method similar to that in Example 132.

Example 133

3-Aminomethyl-N-benzyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxamide hydrochloride
¹H-NMR(DMSO-d₆) δ: 0.93 (6H, d, J=6.6 Hz), 2.11 (1H, m), 3.88 (2H, s), 4.09 (2H, d, J=6.6Hz), 4.36 (2H d, J=6.0Hz), 7.22-7.34 (5H, m), 7.40-7.45 (3H, m), 7.57-7.60 (3H, m), 8.04 (1H, d, J=8.4Hz), 8.41 (1H, d, J=8.4Hz), 8.52 (3H, bs), 9.28 (1H, t, J=6.0Hz).

Example 134

3-Aminomethyl-2-isobutyl-N-methyl-4-phenyl-1(2H)-isoquinolinone-6-carboxamide hydrochloride
¹H-NMR(DMSO-d₆) δ: 0.93 (6H, d, J=6.6 Hz), 2.11 (1H, m), 2.72 (3H, d, J=4.8Hz), 3.87 (2H, s), 4.09 (2H, d, J=6.8Hz), 7.39-7.43 (3H, m), 7.54-7.60 (3H, m), 7.95 (1H, dd, J=8.6, 1.6Hz), 8.39 (1H, d, J=8.6Hz), 8.60 (3H, bs), 8.64 (1H, t, J=4.8Hz).

Example 135

3-Aminomethyl-N-cyclopropyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxamide hydrochloride

¹H-NMR(DMSO-d₆) δ: 0.49-0.59 (2H, m), 0.62-0.71 (2H, m), 0.92 (6H, d, J=6.6 Hz), 2.11 (1H, m), 2.73 (1H, m), 3.88 (2H, s), 4.08 (2H, d, J=7.0Hz), 7.39 (1H, d, J=1.4Hz), 7.40-7.43 (2H, m), 7.58-7.61 (3H, m), 7.94 (1H, dd, J=8.4, 1.4Hz), 8.37 (1H, d, J=8.4Hz), 8.46 (3H, bs), 8.66 (1H, t, J=4.0Hz).

Example 136

¹⁰ **3-Aminomethyl-2-isobutyl-4-phenyl-N-propyl-1(2H)-isoquinolinone-6-carboxamide hydrochloride**
¹H-NMR(DMSO-d₆) δ: 0.83 (3H, t, J=7.4Hz), 0.92 (6H, d, J=6.6 Hz), 1.40-1.60 (2H, m), 2.11 (1H, m), 3.15 (2H, m), 3.88 (2H, s), 4.08 (2H, d, J=7.0Hz), 7.39 (1H, d, J=1.6Hz), 7.39-7.43 (2H, m), 7.57-7.60 (3H, m), 7.97 (1H, dd, J=8.4, 1.6Hz), 8.39 (1H, d, J=8.4Hz), 8.45 (3H, bs), 8.66 (1H, t, J=4.8Hz).

Example 137

3-Aminomethyl-N-ethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxamide hydrochloride
¹H-NMR(DMSO-d₆) δ: 0.92 (6H, d, J=6.6 Hz), 1.07 (3H, t, J=7.0), 2.11 (1H, m), 3.15-3.29 (2H, m), 3.87 (2H, s), 4.08 (2H, d, J=7.0Hz), 7.38-7.43 (3H, m), 7.55-7.63 (3H, m), 7.97 (1H, dd, J=8.4, 1.8Hz), 8.38 (1H, d, J=8.4Hz), 8.45 (3H, bs), 8.68 (1H, t, J=5.0Hz).

Example 138

3-Aminomethyl-N,N-dimethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxamide hydrochloride
¹H-NMR(DMSO-d₆) δ: 0.93 (6H, d, J=6.6 Hz), 2.11 (1H, m), 2.78 (3H, s), 2.91 (3H, s), 3.88 (2H, s), 4.08 (2H, d, J=7.4Hz), 6.84 (1H, d, J=1.0Hz), 7.39-7.43 (2H, m), 7.54-7.61 (4H, m), 8.37 (1H, d, J=8.6Hz), 8.50 (3H, bs).

Example 139

Ethyl N-[(3-aminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-yl)carbony]glycinate hydrochloride
¹H-NMR(DMSO-d₆) δ: 0.93 (6H, d, J=6.6 Hz), 1.17 (3H, t,

J=7.2Hz)', 2.11 (1H, m), 3.88 (2H, s), 3.94 (2H, d,
J=5.6Hz), 4.08 (2H, q, J=7.2Hz), 4.08 (2H, d, J=7.0Hz),
7.39-7.43 (3H, m), 7.57-7.60 (3H, m), 8.00 (1H, dd,
J=8.4, 1.6Hz), 8.43 (1H, d, J=8.4Hz), 8.43 (3H, bs),
5 9.15 (1H, t, J=5.6Hz).

Example 140

3-(Aminomethyl)-6-[(4-hydroxypiperidin-1-yl)carbonyl]-2-isobutyl-4-phenyl-1(2H)-isoquinolinone hydrochloride
¹H-NMR(DMSO-d₆) δ: 0.93 (6H, d, J=6.6 Hz), 1.20-1.80 (6H,
10 m), 2.11 (1H, m), 2.90-3.30 (2H, m), 3.67 (1H, m), 3.89
(2H, s), 4.07 (2H, d, J=6.4Hz), 4.80 (1H, bs), 6.83 (1H,
m), 7.40-7.43 (2H, m), 7.54-7.61 (4H, m), 8.38 (1H, d,
J=8.4Hz), 8.46 (3H, bs).

Example 141

15 3-Aminomethyl-N-(2,2,2-trifluoroethyl)-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxamide hydrochloride
¹H-NMR(DMSO-d₆) δ: 0.93 (6H, d, J=6.6 Hz), 2.12 (1H, m),
3.89 (2H, s), 4.00-4.10 (4H, m), 7.39-7.44 (3H, m),
7.57-7.61 (3H, m), 8.02 (1H, dd, J=8.6, 1.4Hz), 8.44 (1H,
20 d, J=8.4Hz), 8.46 (3H, bs), 9.31 (1H, t, J=6.3Hz)..

Example 142

3-Aminomethyl-4-(4-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone-6-carboxamide hydrochloride
(1) To a solution of 4-bromophthalic anhydride (50 g,
25 220 mmol) in fluorobenzene (300 mL) was added aluminum
chloride (60 g, 450 mmol) by small portions under ice-
cooling. The obtained mixture was stirred at room
temperature for 15 h. The reaction mixture was poured
into ice water and extracted with ethyl acetate. The
30 extract was washed with 1N hydrochloric acid and brine,
dried over anhydrous magnesium sulfate and concentrated
under reduced pressure. The residue was crystallized
from ethyl acetate-diisopropyl ether and the
precipitated crystals were collected by filtration. The
35 crystals were recrystallized from ethyl acetate to give
a solid of a mixture (9:1)(7 g, 10%) of 2-(4-

fluorobenzoyl)-4-bromobenzoic acid and 2-(4-fluorobenzoyl)-5-bromobenzoic acid.

2-(4-fluorobenzoyl)-4-bromobenzoic acid: $^1\text{H-NMR}(\text{CDCl}_3)$ δ : 7.06-7.17 (2H, m), 7.50 (1H, d, $J=2.0\text{Hz}$), 7.69-7.79 (3H, m), 7.95 (1H, d, $J=8.4\text{ Hz}$).

(2) A solid of 6-bromo-4-(4-fluorophenyl)-1*H*-isochromene-3-carboxylic acid (5.5 g, 69%) was obtained from 2-(4-fluorobenzoyl)-4-bromobenzoic acid (7 g, 22 mmol) in the same manner as in Example 106 (2).

10 $^1\text{H-NMR}(\text{CDCl}_3)$ δ : 7.21-7.27 (5H, m), 7.79 (1H, dd, $J=8.4$, 1.8 Hz), 8.27 (1H, d, $J=8.6\text{ Hz}$).

(3) 6-Bromo-4-(4-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone-3-carboxylic acid (5.3 g, 85%) was obtained as crystals from 6-bromo-4-(4-fluorophenyl)-1*H*-isochromene-3-carboxylic acid (5.4 g, 14.9 mmol) in the same manner as in Example 106 (3).

$^1\text{H-NMR}(\text{CDCl}_3)$ δ : 0.94 (6H, d, $J=7.0\text{ Hz}$), 2.28 (1H, m), 4.02 (2H, d; $J=7.4\text{Hz}$), 7.12-7.25 (3H, m), 7.33-7.41 (2H, m), 7.61 (1H, dd, $J=8.4$, 1.8Hz), 8.34 (1H, d, $J=8.4\text{Hz}$).

20 (4) 6-Bromo-4-(4-fluorophenyl)-3-hydroxymethyl-2-isobutyl-1(2H)-isoquinolinone (4.9 g, 96%) was obtained as crystals from 6-bromo-4-(4-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone-3-carboxylic acid (5.3 g, 12.6 mmol) in the same manner as in Example 106 (4).

25 Melting point 194-196°C.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ : 0.98 (6H, d, $J=7.0\text{Hz}$), 1.94 (1H, t, $J=6.0\text{Hz}$), 2.21 (1H, m), 4.20 (2H, d, $J=7.4\text{Hz}$), 4.44 (2H, d, $J=5.6\text{Hz}$), 7.09 (1H, d, $J=1.8\text{Hz}$), 7.18-7.34 (4H, m), 7.52 (1H, dd, $J=8.6$, 1.8Hz), 8.26(1H, d, $J=8.6\text{Hz}$).

30 (5) 6-Bromo-3-chloromethyl-4-(4-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone (4.5 g, 90%) was obtained as crystals from 6-bromo-4-(4-fluorophenyl)-3-hydroxymethyl-2-isobutyl-1(2H)-isoquinolinone (4.8 g, 11.9 mmol) in the same manner as in Example 106 (5).

35 $^1\text{H-NMR}(\text{CDCl}_3)$ δ : 1.01 (6H, d, $J=7.0\text{Hz}$), 2.21 (1H, m), 4.17 (2H, d, $J=7.2\text{Hz}$), 4.36(2H, s), 7.11 (1H, d,

$J=1.8\text{Hz}$), 7.19-7.36 (4H, m), 7.60 (1H, dd, $J=8.4, 1.8\text{Hz}$), 8.34 (1H, d, $J=8.4\text{Hz}$).

(6) 3-(Tert-butoxycarbonylaminomethyl)-6-bromo-4-(4-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone (4.5 g,

5 86%) was obtained as crystals from 6-bromo-3-chloromethyl-4-(4-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone (4.5 g, 10.6 mmol) in the same manner as in Example 106 (6), (7).

^1H NMR (CDCl_3) δ : 0.99 (6H, d, $J=7.0\text{ Hz}$), 1.43 (9H, s), 2.19 (1H, m), 4.05 (2H, d, $J=7.2\text{Hz}$), 4.18 (2H, d, $J=5.0\text{Hz}$), 4.43 (1H, bs), 7.05 (1H, d, $J=1.8\text{Hz}$), 7.21-7.24 (4H, m), 7.56 (1H, dd, $J=8.6, 1.8\text{Hz}$), 8.31 (1H, d, $J=8.6\text{Hz}$).

(7) Methyl 3-(tert-butoxycarbonylaminomethyl)-4-(4-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone-6-carboxylate (1.4 g, 33%) was obtained as crystals from 3-(tert-butoxycarbonylaminomethyl)-6-bromo-4-(4-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone (4.5 g, 8.9 mmol) in the same manner as in Example 107 (2).

20 $^1\text{H-NMR}(\text{CDCl}_3)$ δ : 1.00 (6H, d, $J=7.0\text{Hz}$), 1.43 (9H, s), 2.24 (1H, m), 3.87 (3H, s), 4.08 (2H, d, $J=7.4\text{Hz}$), 4.21 (2H, d, $J=5.0\text{Hz}$), 4.45 (1H, bs), 7.22-7.26 (4H, m), 7.62 (1H, d, $J=2.0\text{Hz}$), 8.05 (1H, dd, $J=8.4, 2.0\text{Hz}$), 8.52 (1H, d, $J=8.4\text{Hz}$).

25 (8) 3-(tert-Butoxycarbonylaminomethyl)-4-(4-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone-6-carboxylic acid (1.1 g, 92%) was obtained as a solid from methyl 3-(tert-butoxycarbonylaminomethyl)-4-(4-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone-6-

30 carboxylate (1.2 g, 2.5 mmol) in the same manner as in Example 108 (1).

$^1\text{H-NMR}(\text{DMSO-d}_6)$ δ : 0.91 (6H, d, $J=6.6\text{ Hz}$), 1.38 (9H, s), 2.17 (2H, m), 3.93 (2H, d, $J=7.6\text{Hz}$), 3.99 (2H, d, $J=4.4\text{Hz}$), 7.33 (1H, bs), 7.37-7.48 (4H, m), 7.51 (1H, d, $J=1.4\text{H}$), 8.00 (1H, dd, $J=8.4, 1.4\text{Hz}$), 8.40 (1H, d, $J=8.4\text{Hz}$).

(9) 3-(Tert-butoxycarbonylaminomethyl)-4-(4-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone-6-carboxamide (0.57 g, 95%) was obtained as a solid from 3-(tert-butoxycarbonylaminomethyl)-4-(4-fluorophenyl)-2-

5 isobutyl-1(2H)-isoquinolinone-6-carboxylic acid (0.6 g, 1.3 mmol) in the same manner as in Example 109 (1).

¹H-NMR(CDCl₃) δ: 1.00 (6H, d, J=7.0Hz), 1.44 (9H, s), 2.26 (2H, m), 4.07 (2H, d, J=6.8Hz), 4.20 (2H, d, J=4.8Hz), 4.62 (1H, bs), 5.12 (1H, bs), 6.03 (1H, bs),

10 7.22-7.26 (4H, m), 7.38 (1H, s), 7.74 (1H, d, J=8.0Hz), 8.44 (1H, bs).

(10) To a solution of 3-(tert-butoxycarbonylaminomethyl)-4-(4-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone-6-carboxamide (0.5 g, 1.1 mmol) in tetrahydrofuran (2 mL) was added a solution of 4N hydrogen chloride in ethyl acetate (10 mL). The obtained solution was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure and the residue was crystallized from diethyl ether to give 3-aminomethyl-4-(4-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone-6-carboxamide hydrochloride (0.37 g, 85%) as crystals.

Melting point 218-220°C.

¹H-NMR(DMSO-d₆) δ: 0.92 (6H, d, J=6.6Hz), 2.10 (1H, m), 3.86 (2H, d, J=4.6Hz), 4.08 (2H, d, J=7.4Hz), 7.36-7.46 (5H, m), 7.59 (1H, s), 8.00 (1H, dd, J=8.4, 1.6Hz), 8.17 (1H, s), 8.37 (1H, d, J=8.4Hz), 8.55 (3H, bs).

Example 143

Methyl 3-aminomethyl-4-(4-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone-6-carboxylate hydrochloride

This compound was synthesized from methyl 3-(tert-butoxycarbonylaminomethyl)-4-(4-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone-6-carboxylate in the same manner as in Example 142(10).

¹H-NMR(DMSO-d₆) δ: 0.93 (6H, d, J=6.6 Hz), 2.11 (1H, m), 3.81 (3H, s), 3.88 (2H, s), 4.08 (2H, d, J=7.8Hz), 7.39-

7.52 (5H, m), 8.08 (1H, dd, J=8.4, 1.6Hz), 8.46 (1H, d, J=8.4 Hz), 8.50 (3H, s).

Example 144

- 3-Aminomethyl-4-(4-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone-6-carboxylic acid hydrochloride
 This compound was synthesized from 3-(tert-butoxycarbonylaminomethyl)-4-(4-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone-6-carboxylic acid in the same manner as in Example 142(10).
¹⁰ $^1\text{H-NMR}(\text{DMSO-d}_6)$ δ : 0.93 (6H, d, J=6.6 Hz), 2.14 (1H, m), 3.89 (2H, s), 4.08 (1H, s, J=7.8Hz), 7.39-7.52 (5H, m), 8.06 (1H, dd, J=8.4, 1.6Hz), 8.44 (1H, d, J=8.4Hz), 8.50 (3H, bs).

Example 145

- 3-Aminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxamide [3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinecarboxamide]

To a solution of 3-aminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxamide hydrochloride (2.04 g, 5 mmol) in water (20 mL) was added 1N sodium hydroxide (10 mL) and the obtained mixture was stirred at room temperature for 10 min. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate to give 3-aminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxamide (0.87 g, 82.9%) as crystals.

³⁰ Melting point 208°C.

Elemental analysis for $\text{C}_{21}\text{H}_{23}\text{N}_3\text{O}_2$

Calculated: C, 72.18; H, 6.63; N, 12.03.

Found: C, 72.10; H, 6.56; N, 11.88.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ : 1.01 (6H, d, J=6.6 Hz), 1.42 (2H, bs), 2.20-2.34 (1H, m), 3.68 (2H, s), 4.23 (2H, d, J=7.6 Hz), 5.72 (1H, bs), 6.01 (1H, bs), 5.89 (1H, bs), 7.26-7.31

(2H, m), 7.20 (1H, d, J=2.2 Hz), 7.46-7.57 (3H, m), 7.79 (1H, dd, J=1.8, 8.4 Hz), 8.54 (1H, d, J=8.4 Hz).

Powder X-ray crystal diffraction data

Diffraction angle: 2θ(°) spacing: d value

5 (angstrom)

5.98	14.8
7.88	11.2
8.44	10.5
17.1	5.19

10 Recrystallization from ethyl acetate in the same manner gave crystals in a different crystal form.

Powder X-ray crystal diffraction data

Diffraction angle: 2θ(°) spacing: d value

(angstrom)

15	7.22	11.4
	9.80	9.02
	12.1	7.32
	13.5	6.53
	17.9	4.94
20	19.6	4.52
	20.6	4.30
	21.8	4.08

Example 146

3-(Aminomethyl)-4-butoxy-2-cyclopropylmethyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxamide hydrochloride

25 (1) A solution of 4-bromophthalic anhydride (22.70 g, 100 mmol) and ethyl 2-(cyclopropylmethylamino)acetate (18.87 g, 120 mmol) in tetrahydrofuran (150 mL) was stirred at room temperature for 1 h. The reaction

30 mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in N,N-dimethylformamide (150 mL), and potassium carbonate

35 (14.82 g, 100 mmol) and ethyl iodide (9.6 mL, 120 mmol) were added thereto. The mixture was stirred at room

temperature for 12 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in ethanol (150 mL) and 20% sodium ethoxide ethanol solution (68.10 g, 200 mmol) was added thereto. The mixture was stirred at room temperature for 1 h. The reaction mixture was poured into 1N hydrochloric acid (300 mL) and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography and the component eluted earlier was concentrated to give ethyl 7-bromo-2-cyclopropylmethyl-4-hydroxy-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (11.14 g, 30.4%) as crystals. Melting point 105-105.5°C.

Elemental analysis for $C_{16}H_{16}NO_4Br$

Calculated: C, 52.48; H, 4.40; N, 3.82.

Found: C, 52.50; H, 4.31; N, 3.80..
 1H -NMR(CDCl₃) δ: 0.32-0.54 (4H, m), 0.97-1.14 (1H, m), 1.47 (3H, t, J=7.2 Hz), 4.34 (2H, d, J=7.0 Hz), 4.45 (2H, d, J=7.2 Hz), 7.85 (1H, dd, J=2.0, 8.6 Hz), 8.02 (1H, d, J=8.6 Hz), 8.59 (1H, d, J=2.6 Hz), 11.25 (1H, s).

The component eluted later was concentrated to give ethyl 6-bromo-2-cyclopropylmethyl-4-hydroxy-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (11.02 g, 30.1%) as crystals.

Melting point 64-65°C.

Elemental analysis for $C_{16}H_{16}NO_4Br$

Calculated: C, 52.48; H, 4.40; N, 3.82.

Found: C, 52.36; H, 4.31; N, 3.87.

1H -NMR(CDCl₃) δ: 0.32-0.54 (4H, m), 0.97-1.13 (1H, m), 1.48 (3H, t, J=7.2 Hz), 4.33 (2H, d, J=6.6 Hz), 4.52 (2H, d, J=7.2 Hz), 7.78 (1H, dd, J=2.0, 8.5 Hz), 8.29 (1H, d, J=8.5 Hz), 8.30 (1H, d, J=2.0 Hz), 11.16 (1H, s).

(2) To a solution of ethyl 6-bromo-2-cyclopropylmethyl-4-hydroxy-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (7.32 g, 20 mmol), 1-butanol (2.7 mL, 30 mmol) and tributylphosphine (10.0 mL, 40 mmol) in tetrahydrofuran (100 mL) was added 1,1'-(azodicarbonyl)dipiperidine (10.09 g, 40 mmol) and the mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography to give

10 ethyl 6-bromo-4-butoxy-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (7.24 g, 85.8%) as an oil.

¹H-NMR(CDCl₃) δ: 0.39-0.57 (4H, m), 1.02 (3H, t, J=7.1 Hz), 1.13-1.31 (1H, m), 1.45 (3H, t, J=7.2 Hz), 1.46-1.63 (2H, m), 1.73-1.87 (2H, m), 3.90 (2H, d, J=7.0 Hz), 3.96 (2H, t, J=6.6 Hz), 4.47 (2H, q, J=7.2 Hz), 7.65 (1H, dd, J=2.0, 8.6 Hz), 7.78 (1H, d, J=2.0 Hz), 8.29 (1H, dd, J=5.4, 8.6 Hz).

(3) To a solution of ethyl 6-bromo-4-butoxy-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (7.18 g, 17 mmol) in tetrahydrofuran (20 mL) and ethanol (20 mL) was added an aqueous solution (10 mL) of sodium hydroxide (2.04 g, 51 mmol). The obtained mixture was refluxed under heating for 12 h. The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals was recrystallized from ethyl acetate - diisopropyl ether to give 6-bromo-4-butoxy-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (6.41 g, 95.7%) as crystals.

Melting point 166-167°C.
35 Elemental analysis for C₁₈H₂₀NO₄Br
Calculated: C, 54.84; H, 5.11; N, 3.55.

Found: C, 54.78; H, 4.98; N, 3.27.

¹H-NMR(CDCl₃) δ: 0.41-0.57 (4H, m), 1.00 (3H, t, J=7.4 Hz), 1.22-1.35 (1H, m), 1.45-1.63 (2H, m), 1.75-1.89 (2H, m), 3.98-4.08 (4H, m), 7.63 (1H, dd, J=1.8, 8.8 Hz),

⁵ 7.68 (1H, bs), 7.82 (1H, d, J=1.8 Hz), 8.24 (1H, d, J=8.8 Hz).

(4) To a solution of 6-bromo-4-butoxy-2-

cyclopropylmethyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (6.31 g, 16 mmol) in

¹⁰ tetrahydrofuran (50 mL) were added oxalyl chloride (1.7 mL, 19.2 mmol) and N,N-dimethylformamide (2 drops), and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in

¹⁵ tetrahydrofuran (20 mL). The obtained solution was added dropwise to a suspension of sodium tetrahydroborate (2.11 g, 56 mmol) in 1,2-dimethoxyethane (30 mL) at 0°C. The obtained mixture was stirred at 0°C for 1 h. The reaction mixture was poured ²⁰ into 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give ²⁵ 6-bromo-4-butoxy-2-cyclopropylmethyl-3-hydroxymethyl-1(2H)-isoquinolinone (5.87 g, 96.5%) as crystals.

Melting point 111-112°C.

Elemental analysis for C₁₈H₂₂NO₃Br

³⁰ Calculated: C, 56.85; H, 5.83; N, 3.68.

Found: C, 56.69; H, 5.67; N, 3.59.

¹H-NMR(CDCl₃) δ: 0.42-0.58 (4H, m), 1.04 (3H, t, J=7.1 Hz), 1.12-1.25 (1H, m), 1.49-1.68 (2H, m), 1.79-1.93 (2H, m), 2.48 (1H, bs), 3.88 (2H, t, J=6.6 Hz), 4.19 (2H, d, J=6.6 Hz), 4.83 (2H, s), 7.56 (1H, dd, J=2.0, 8.6Hz),

³⁵ 7.79 (1H, d, J=2.0 Hz), 8.20 (1H, d, J=8.8 Hz).

(5) To a solution of 6-bromo-4-butoxy-2-cyclopropylmethyl-3-hydroxymethyl-1(2H)-isoquinolinone (5.70 g, 15 mmol) in toluene (50 mL) was added thionyl chloride (2.2 mL, 30 mmol). The obtained mixture was
5 refluxed under heating for 2 h. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution, and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under
10 reduced pressure to give 6-bromo-4-butoxy-3-chloromethyl-2-cyclopropylmethyl-1(2H)-isoquinolinone (5.72 g, 95.7%) as crystals.

¹H-NMR(CDCl₃) δ: 0.44-0.61 (4H, m), 1.02-1.30 (4H, m), 1.53-1.68 (2H, m), 1.71-1.97 (2H, m), 4.00 (2H, t, J=6.4 Hz), 4.21 (2H, d, J=6.6 Hz), 4.84 (2H, s), 7.63 (1H, dd, J=1.8, 8.4 Hz), 7.88 (1H, d, J=1.8 Hz), 8.29 (1H, d, J=8.4 Hz).

(6) A solution of 6-bromo-4-butoxy-3-chloromethyl-2-cyclopropylmethyl-1(2H)-isoquinolinone (5.58 g, 14 mmol)
20 and potassium phthalimide (3.89 g, 21 mmol) in N,N-dimethylformamide (50 mL) was stirred at room temperature for 5 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from tetrahydrofuran - n-hexane to give
25 2-[(6-bromo-4-butoxy-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isouinolinyl)methyl]-1H-isoindole-1,3(2H)-dione (6.57 g, 94.7%) as crystals.
Melting point 156-157°C.
Elemental analysis for C₂₆H₂₅N₂O₄Br
Calculated: C, 61.30; H, 4.95; N, 5.50.
Found: C, 61.39; H, 5.06; N, 5.47.
30 ¹H-NMR(CDCl₃) δ: 0.45-0.50 (4H, m), 0.97-1.08 (4H, m), 1.44-1.61 (1H, m), 1.79-1.93 (2H, m), 3.99 (2H, t, J=6.7

Hz), 4.16 (2H, d, J=6.2 Hz), 5.07 (2H, s), 7.59 (1H, dd, J=2.0, 8.8 Hz), 7.71-7.85 (4H, m), 7.86 (1H, d, J=2.0 Hz), 8.27 (1H, d, J=8.8 Hz).

- (7) To a solution of 2-[(6-bromo-4-butoxy-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl]-1H-isoindole-1,3(2H)-dione (6.62 g, 13 mmol) in ethanol (50 mL) was added hydrazine monohydrate (0.13 mL, 2.7 mmol). The obtained mixture was refluxed under heating for 1 h. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (30 mL) and di-t-butyl dicarbonate (4.5 mL, 19.5 mmol) was added thereto. The obtained mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - n-hexane to give tert-butyl (6-bromo-4-butoxy-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (4.41 g, 70.8%) as crystals.

Melting point 118-119°C.

Elemental analysis for C₂₃H₃₁N₂O₄Br

Calculated: C, 57.62; H, 6.52; N, 5.84.

Found: C, 57.79; H, 6.37; N, 5.71.

- (8) A mixture of tert-butyl (6-bromo-4-butoxy-2-
- ¹H-NMR(CDCl₃) δ: 0.50-0.55 (4H, m), 1.05 (3H, t, J=7.3 Hz), 1.13-1.26 (1H, m), 1.46 (9H, s), 1.47-1.68 (2H, m), 1.80-1.94 (2H, m), 3.86 (2H, t, J=6.5 Hz), 4.09 (2H, d, J=7.0 Hz), 4.53 (2H, d, J=5.6 Hz), 4.79 (1H, bs), 7.58 (1H, dd, J=2.0, 8, 6 Hz), 7.82 (1H, d, J=2.0 Hz), 8.26 (1H, d, J=8.6 Hz).

cyclopropylmethyl-1-oxo-1,2-dihydro-3-isouquinolinyl)-methylcarbamate (4.08 g, 8.5 mmol), 1,3-bis(diphenylphosphino)propane (0.35 g, 0.85 mmol) and triethylamine (1.3 mL, 9.4 mmol) in dimethyl sulfoxide (60 mL) and methanol (40 mL) was stirred under a carbon monoxide atmosphere at room temperature for 30 min. To the obtained mixture was added palladium acetate (0.19 g, 0.85 mmol) and the mixture was stirred under a carbon monoxide atmosphere at 70°C for 15 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give methyl 4-butoxy-3-[[(tert-butoxycarbonyl)amino]methyl]-2-cyclopropylmethyl-1-oxo-1,2-dihydro-6-isouquinolinecarboxylate (3.41 g, 87.7%) as crystals. Melting point 139-140°C.

Elemental analysis for C₂₅H₃₄N₂O₆

Calculated: C, 65.48; H, 7.47; N, 6.11.
Found: C, 65.59; H, 7.53; N, 6.13.
¹H-NMR (CDCl₃) δ: 0.52-0.55 (4H, m), 1.06 (3H, t, J=7.4 Hz), 1.15-1.30 (1H, m), 1.46 (9H, s), 1.53-1.68 (2H, m), 1.83-1.97 (2H, m), 3.91 (2H, t, J=6.4 Hz), 3.99 (3H, s), 3.91 (2H, d, J=6.6 Hz), 4.56 (2H, d, J=5.4 Hz), 4.81 (1H, bs), 8.09 (1H, dd, J=1.6, 8.4 Hz), 8.40 (1H, d, J=1.6 Hz), 8.48 (1H, d, J=8.4 Hz).

(9) To a solution of methyl 4-butoxy-3-[[(tert-butoxycarbonyl)amino]methyl]-2-cyclopropylmethyl-1-oxo-1,2-dihydro-6-isouquinolinecarboxylate (2.98 g, 6.5 mmol) in tetrahydrofuran (10 mL) and methanol (10 mL) was added 1N sodium hydroxide (10 mL). The obtained mixture was stirred at room temperature for 2 h. The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous

magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give 4-butoxy-3-[(tert-butoxycarbonyl)amino]methyl]-2-
cyclopropylmethyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid (2.62 g, 90.7%) as crystals. Melting point 197-198°C.

Elemental analysis for $C_{24}H_{32}N_2O_6$

Calculated: C, 64.85; H, 7.26; N, 6.30.

Found: C, 64.95; H, 7.26; N, 6.29.

1H -NMR(CDCl₃). δ : 0.51-0.53 (4H, m), 1.07 (3H, t, J=7.3 Hz), 1.13-1.30 (1H, m), 1.50 (9H, s), 1.53-1.72 (2H, m), 1.85-1.99 (2H, m), 3.91 (2H, t, J=6.2 Hz), 4.09 (2H, d, J=6.6 Hz), 4.56 (2H, d, J=5.0 Hz), 4.47 (1H, bs), 8.08 (1H, d, J=8.5 Hz), 8.30 (1H, bs), 8.39 (1H, d, J=8.5 Hz).

(10) A solution of 4-butoxy-3-[(tert-butoxycarbonyl)amino]methyl]-2-cyclopropylmethyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid (0.89 g, 2 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.77 g, 4 mmol) and 1-hydroxybenzotriazole ammonium salt (0.61 g, 4 mmol) in N,N-dimethylformamide (10 mL) was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give 4-butoxy-3-[(tert-butoxycarbonyl)amino]methyl]-2-
cyclopropylmethyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxamide (0.82 g, 93.2%) as crystals.

Melting point 202-203°C.

Elemental analysis for $C_{24}H_{33}N_3O_5$

Calculated: C, 64.99; H, 7.50; N, 9.47.

Found: C, 64.89; H, 7.68; N, 9.42.

1H -NMR(CDCl₃). δ : 0.52-0.56 (4H, m), 1.03 (3H, t, J=7.1

Hz), 1.18-1.29 (1H, m), 1.48 (9H, s), 1.49-1.66 (2H, m), 1.86-1.94 (2H, m), 3.87 (2H, t, J=6.6 Hz), 4.10 (2H, d, J=6.6 Hz), 4.54 (2H, d, J=5.4 Hz), 5.24 (1H, bs), 6.03 (1H, bs), 6.60 (1H, bs), 7.72 (1H, dd, J=1.6, 8.4 Hz),

5 8.04 (1H, d, J=1.6 Hz), 8.29 (1H, d, J=8.4 Hz).

(11) To a solution of 4-butoxy-3-[(tert-butoxycarbonyl)amino]methyl-2-cyclopropylmethyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxamide (0.27 g, 0.6 mmol) in ethyl acetate (5 mL) was added a solution of 4N

10 hydrogen chloride in ethyl acetate (5 mL) and the obtained solution was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the precipitated crystals were recrystallized from methanol-diethyl ether to give

15 3-(aminomethyl)-4-butoxy-2-cyclopropylmethyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxamide hydrochloride (0.21 g, 91.3%) as crystals.

Melting point 164-165°C.

Elemental analysis for C₁₉H₂₆N₃O₃Cl 0.5H₂O

20 Calculated: C, 58.68; H, 7.00; N, 10.81.

Found: C, 59.03; H, 6.85; N, 10.82.

¹H-NMR(DMSO-d₆) δ: 0.45-0.49 (4H, m), 1.01 (3H, t, J=7.3 Hz), 1.09-1.21 (1H, m), 1.52-1.63 (2H, m), 1.83-1.99 (2H, m), 3.99 (2H, t, J=5.9 Hz), 4.08 (2H, d, J=6.4 Hz), 4.23

25 (2H, s), 7.71 (1H, s), 8.05 (1H, d, J=8.2 Hz), 8.23 (1H, s), 8.33 (1H, d, J=8.2 Hz), 8.38 (1H, s), 8.68 (3H, bs).

Example 147

3-(Aminomethyl)-4-butoxy-2-cyclopropylmethyl-6-(1,3-oxazol-5-yl)-1(2H)-isoquinolinone hydrochloride

30 (1) To a solution of 4-butoxy-3-[(tert-butoxycarbonyl)amino]methyl-2-cyclopropylmethyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid (Example 146 (9)) (0.45 g, 3.5 mmol) and N-methylmorpholine (0.13 mL, 1.2 mmol) in tetrahydrofuran (10 mL) was added ethyl

35 chloroformate (0.12 mL, 1.2 mmol) at 0°C, and the mixture was stirred at 0°C for 10 min. To the obtained

mixture were added sodium tetrahydroborate (0.11 g, 3 mmol) and methanol (5 mL), and the mixture was stirred at 0°C for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was
5 washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The precipitated crystals were recrystallized from ethyl acetate - diisopropyl ether to give tert-butyl (4-butoxy-2-cyclopropylmethyl-6-hydroxymethyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.33 g, 76.7%)
10 as crystals.

Melting point 171-172°C.

Elemental analysis for C₂₄H₃₄N₂O₅

Calculated: C, 66.95; H, 7.96; N, 6.51.

15 Found: C, 66.65; H, 7.82; N, 6.63.

¹H-NMR(CDCl₃) δ: 0.51-0.56 (4H, m), 1.00 (3H, t, J=7.3 Hz), 1.19-1.26 (1H, m), 1.49-1.57 (11H, m), 1.79-1.93 (2H, m), 2.27 (1H, bs), 3.82 (2H, t, J=6.8 Hz), 4.07 (2H, d, J=6.6 Hz), 4.51 (2H, d, J=5.4 Hz), 4.80 (2H, s), 5.53 (1H, s), 7.38 (1H, d, J=8.2 Hz), 7.46 (1H, s), 8.13 (1H, d, J=8.2 Hz).

(2) To a solution of 4 tert-butyl (4-butoxy-2-cyclopropylmethyl-6-hydroxymethyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.45 g, 3.5 mmol) in
25 tetrahydrofuran (10 mL) was added manganese dioxide (0.12 g) and the mixture was stirred at room temperature for 12 h. Manganese dioxide was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl (4-butoxy-2-cyclopropylmethyl-6-formyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.33 g, 76.7%) as crystals.

Melting point 151-152°C.

Elemental analysis for C₂₄H₃₂N₂O₅

30 Calculated: C, 67.27; H, 7.53; N, 6.54.

Found: C, 67.08; H, 7.55; N, 6.54.

¹H-NMR(CDCl₃) δ: 0.53-0.56 (4H, m), 1.06 (3H, t, J=7.3 Hz), 1.16-1.28 (1H, m), 1.47 (9H, s), 1.55-1.68 (2H, m), 1.87-1.96 (2H, m), 3.92 (2H, t, J=6.4 Hz), 4.14 (2H, d, J=6.6 Hz), 4.57 (2H, d, J=5.7 Hz), 4.82 (1H, bs), 7.96 (1H, dd, J=1.8, 8.4 Hz), 8.19 (1H, d, J=1.8 Hz), 8.57 (1H, d, J=8.4 Hz), 10.19 (1H, s).

(3) A solution of tert-butyl (4-butoxy-2-cyclopropylmethyl-6-formyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.34 g, 0.8 mmol), p-toluenesulfonylmethyl isocyanide (0.16 g, 0.8 mmol) and potassium carbonate (0.22 g, 1.6 mmol) in methanol (10 mL) was refluxed under heating for 30 min. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography and the precipitated crystals were recrystallized from ethyl acetate-diisopropyl ether to give tert-butyl [4-butoxy-2-cyclopropylmethyl-6-(1,3-oxazol-5-yl)-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.33 g, 76.7%) as crystals.

Melting point 160-161°C.

Elemental analysis for C₂₆H₃₃N₃O₅

Calculated: C, 66.79; H, 7.11; N, 8.99.
 Found: C, 66.63; H, 7.14; N, 9.01.

¹H-NMR(CDCl₃) δ: 0.52-0.56 (4H, m), 1.07 (3H, t, J=7.2 Hz), 1.12-1.26 (1H, m), 1.47 (9H, s), 1.58-1.71 (2H, m), 1.87-1.96 (2H, m), 3.92 (2H, t, J=6.6 Hz), 4.12 (2H, d, J=6.6 Hz), 4.56 (2H, d, J=5.7 Hz), 4.84 (1H, bs), 7.53 (1H, s), 7.75 (1H, dd, J=1.5, 8.4 Hz), 7.97 (1H, d, J=1.5 Hz), 8.02 (1H, s), 8.46 (1H, d, J=8.4 Hz).

(4) To a solution of tert-butyl [4-butoxy-2-cyclopropylmethyl-6-(1,3-oxazol-5-yl)-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.19 g, 0.4 mmol) in ethyl acetate (5 mL) was added a solution of 4N hydrogen

chloride in ethyl acetate (5 mL) and the obtained solution was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the precipitated crystals were recrystallized from methanol-diethyl ether to give 3-(aminomethyl)-4-butoxy-2-cyclopropylmethyl-6-(1,3-oxazol-5-yl)-1(2H)-isoquinolinone hydrochloride (0.15 g, 93.8%) as crystals. Melting point 124-126°C.

Elemental analysis for $C_{21}H_{26}N_3O_3Cl$ 1.25H₂O

Calculated: C, 59.15; H, 6.74; N, 9.85.

Found: C, 59.12; H, 6.58; N, 9.71.

¹H-NMR(DMSO-d₆) δ: 0.46-0.49 (4H, s), 1.03 (3H, t, J=7.2 Hz), 1.15-1.28 (1H, m), 1.54-1.69 (2H, m), 1.83-1.95 (2H, m), 3.99 (2H, t, J=6.2 Hz), 4.08 (2H, d, J=6.6 Hz), 4.23 (2H, d, J=5.4 Hz), 7.99-8.01 (3H, m), 8.36 (1H, d, J=9.2 Hz), 8.63 (1H, s), 8.74 (3H, bs).

Example 148

(E)-3-[3-(Aminomethyl)-4-butoxy-2-cyclopropylmethyl-1-oxo-1,2-dihydro-6-isooquinolinyl]-2-propenamide

hydrochloride

(1) To a solution of ethyl diethylphosphonoacetate (0.99 mL, 5 mmol) in N,N-dimethylformamide (30 mL) was added sodium hydride (0.20 g, 5 mmol)(60% in oil) and the mixture was stirred at room temperature for 10 min. To the obtained mixture was added a solution of tert-butyl (4-butoxy-2-cyclopropylmethyl-6-formyl-1-oxo-1,2-dihydro-3-isooquinolinyl)methylcarbamate (Example 2 (2))(2.14 g, 5 mmol) in N,N-dimethylformamide (20 mL) and the mixture was stirred at room temperature for 3 h.

The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give

ethyl (E)-3-(4-butoxy-3-[(tert-butoxycarbonyl)amino]methyl]-2-cyclopropylmethyl-1-oxo-

1,2-dihydro-3-isoquinolinyl)-2-propenate (1.92 g, 77.1%) as crystals.

Melting point 166-167°C.

Elemental analysis for C₂₈H₃₈N₂O₆

- 5 Calculated: C, 67.45; H, 7.68; N, 5.62.
 Found: C, 67.40; H, 7.65; N, 5.44.
¹H-NMR(CDCl₃) δ: 0.51-0.55 (4H, m), 1.06 (3H, t, J=7.1 Hz), 1.14-1.27 (1H, m), 1.37 (3H, t, J=7.2 Hz), 1.46 (9H, s), 1.47-1.69 (2H, m), 1.83-1.97 (2H, m), 3.89 (2H, t, J=6.4 Hz), 4.12 (2H, d, J=6.6 Hz), 4.30 (2H, q, J=7.2 Hz), 4.55 (2H, d, J=5.4 Hz), 4.78 (1H, bs), 6.58 (1H, d, J=15.8 Hz), 7.66 (1H, dd, J=1.8, 8.4 Hz), 7.78 (1H, d, J=1.8 Hz), 7.79 (1H, d, J=15.8 Hz), 8.42 (1H, d, J=8.4 Hz).
- 15 (2) To a solution of ethyl (E)-3-(4-butoxy-3-[(tert-butoxycarbonyl)amino]methyl]-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isoquinolinyl)-2-propenate (1.00 g, 2 mmol) in tetrahydrofuran (10 mL) and ethanol (10 mL) was added 1N sodium hydroxide (4 mL). The obtained mixture
 20 was stirred at room temperature for 2 h. The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from tetrahydrofuran - diisopropyl ether to give (E)-3-(4-butoxy-3-[(tert-butoxycarbonyl)amino]methyl]-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isoquinolinyl)-2-propenic acid (0.92 g, 97.9%) as crystals.
- 30 Melting point 229-230°C.
- Elemental analysis for C₂₆H₃₄N₂O₆
 Calculated: C, 66.36; H, 7.28; N, 5.95.
 Found: C, 66.05; H, 7.22; N, 5.66.
¹H-NMR(CDCl₃) δ: 0.50-0.55 (4H, m), 1.07 (3H, t, J=7.3 Hz), 1.12-1.28 (1H, m), 1.48 (9H, s), 1.49-1.70 (2H, m), 1.84-1.98 (2H, m), 3.89 (2H, t, J=6.6 Hz), 4.10 (2H, d,

J=6.6 Hz), 4.55 (2H, d, J=5.0 Hz), 5.12 (1H, bs), 6.59 (1H, d, J=16.0 Hz), 7.64 (1H, d, J=8.2 Hz), 7.73 (1H, s), 7.85 (1H, d, J=16.0 Hz), 8.38 (1H, d, J=8.2 Hz).

(3) A solution of (E)-3-(4-butoxy-3-[(tert-

butoxycarbonyl)amino]methyl]-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isquinolinyl)-2-propenic acid (0.71 g, 1.5 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.58 g, 3 mmol) and 1-hydroxybenzotriazole ammonium salt (0.46 g, 3 mmol) in N,N-dimethylformamide (10 mL) was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from tetrahydrofuran - diisopropyl ether to give (E)-3-(4-butoxy-3-[(tert-butoxycarbonyl)amino]methyl]-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isquinolinyl)-2-propenamide (0.67 g, 95.7%) as crystals.

Melting point 198-199°C.

Elemental analysis for C₂₆H₃₅N₃O₅ 0.5H₂O

Calculated: C, 65.87; H, 7.55; N, 8.86

Found: C, 65.86; H, 7.89; N, 8.68

¹H-NMR(CDCl₃) δ: 0.50-0.54 (4H, m), 1.04 (3H, t, J=7.4

Hz), 1.12-1.26 (1H, m), 1.47 (9H, s), 1.48-1.67 (2H, m), 1.81-1.95 (2H, m), 3.88 (2H, t, J=6.4 Hz), 4.10 (2H, d, J=6.6 Hz), 4.54 (2H, d, J=5.2 Hz), 5.40 (1H, bs); 5.89 (1H, bs), 6.05 (1H, bs), 6.60 (1H, d, J=15.8 Hz), 7.56 (1H, dd, J=1.5, 8.4 Hz), 7.69 (1H, d, J=1.5 Hz), 7.73 (1H, d, J=15.8 Hz), 8.31 (1H, d, J=8.4 Hz).

(4) To a solution of (E)-3-(4-butoxy-3-[(tert-

butoxycarbonyl)amino]methyl]-1-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isquinolinyl)-2-propenamide (0.38 g, 0.8 mmol) in ethyl acetate (5 mL) was added a solution of 4N

hydrogen chloride in ethyl acetate (5 mL) and the obtained solution was stirred at room temperature for 2

h. The reaction mixture was concentrated under reduced pressure, and the precipitated crystals were recrystallized from methanol - diisopropyl ether to give (E)-3-[3-(aminomethyl)-4-butoxy-2-cyclopropylmethyl-1-
5 oxo-1,2-dihydro-6-isooquinolinyl]-2-propenamide hydrochloride (0.31 g, 96.9%) as crystals.
Melting point 188-190°C.

Elemental analysis for $C_{21}H_{28}N_3O_3Cl \cdot 2H_2O$

Calculated: C, 57.07; H, 7.30; N, 9.51.

10 Found: C, 56.82; H, 7.06; N, 9.49.

1H -NMR(DMSO- d_6) δ : 0.45-0.48 (4H, m), 1.02 (3H, t, J=6.9 Hz), 1.13-1.24 (1H, m), 1.47-1.69 (2H, m), 1.79-1.99 (2H, m), 4.05 (2H, bs), 4.22 (2H, bs), 4.32 (2H, bs), 6.85 (1H, d, J=15.4 Hz), 7.28 (1H, bs), 7.63 (1H, d, J=15.4

15 Hz), 7.80-7.88 (3H, m), 8.30 (1H, d, J=7.0 Hz), 8.68 (3H, bs).

Example 149

2-[[3-(Aminomethyl)-4-butoxy-2-cyclopropylmethyl-1-oxo-
1,2-dihydro-6-isooquinolinyl]oxy]acetamide hydrochloride

20 (1) A solution of 4-fluorophthalic anhydride (24.99 g, 150 mmol) and ethyl 2-(cyclopropylmethylamino)acetate (23.58 g, 150 mmol) in tetrahydrofuran (200 mL) was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate.

25 The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in N,N-dimethylformamide (200 mL) and potassium carbonate (20.73 g, 150 mmol) and ethyl iodide (14.4 mL, 180 mmol)

30 were added. The mixture was stirred at room temperature for 3 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was

35 dissolved in ethanol (300 mL) and a solution of 20% sodium ethoxide ethanol solution (102 g, 300 mmol) was

added thereto. The mixture was stirred at room temperature for 1 h. The reaction mixture was poured into 1N hydrochloric acid (300 mL) and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography and the component eluted earlier was concentrated to give ethyl 2-cyclopropylmethyl-7-fluoro-4-hydroxy-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (13.11 g, 28.6%) as crystals. Melting point 88-89°C.

Elemental analysis for C₁₆H₁₆NO₄F

Calculated: C, 62.94; H, 5.28; N, 4.59.

Found: C, 62.96; H, 5.23; N, 4.61.

¹H-NMR(CDCl₃) δ: 0.34-0.52 (4H, m), 1.04-1.13 (1H, m), 1.48 (3H, t, J=7.2 Hz), 4.35 (2H, d, J=6.9 Hz), 4.51 (2H, d, J=7.2 Hz), 7.44-7.50 (1H, m), 8.09 (1H, dd, J=2.6, 6.2 Hz), 8.19 (1H, dd, J=6.2, 8.4 Hz), 11.36 (1H, s).

The component eluted later was concentrated to give ethyl 2-cyclopropylmethyl-6-fluoro-4-hydroxy-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (9.34 g, 20.4%) as crystals.

Melting point 61-62°C.

Elemental analysis for C₁₆H₁₆NO₄F

Calculated: C, 62.94; H, 5.28; N, 4.59.

Found: C, 62.75; H, 5.14; N, 4.64.

¹H-NMR(CDCl₃) δ: 0.32-0.54 (4H, m), 1.00-1.16 (1H, m), 1.48 (3H, t, J=7.2 Hz), 4.33 (2H, d, J=7.0 Hz), 4.52 (2H, d, J=7.2 Hz), 7.33-7.43 (1H, m), 7.78 (1H, dd, J=2.6, 9.2 Hz), 8.46 (1H, dd, J=5.4, 8.8 Hz), 11.14 (1H, s).

(2) To a solution of ethyl 2-cyclopropylmethyl-6-fluoro-4-hydroxy-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (9.16 g, 30 mmol), 1-butanol (3.3 mL, 45 mmol) and tributylphosphine (14.9 mL, 60 mmol) in tetrahydrofuran (100 mL) was added 1,1'-(azodicarbonyl)dipiperidine (15.14 g, 60 mmol) and the mixture was stirred at room

temperature for 3 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography to give ethyl 4-butoxy-2-cyclopropylmethyl-6-fluoro-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (9.24 g, 85.2%) as an oil.

¹H-NMR(CDCl₃) δ: 0.39-0.57 (4H, m), 1.01 (3H, t, J=7.3 Hz), 1.12-1.21 (1H, m), 1.41-1.62 (5H, m), 1.73-1.87 (2H, m), 3.91 (2H, d, J=6.8 Hz), 3.96 (2H, t, J=6.6 Hz), 4.47 (2H, q, J=7.3 Hz), 7.19-7.30 (1H, m), 8.73 (1H, dd, J=2.4, 9.4 Hz), 8.46 (1H, dd, J=5.4, 8.8 Hz).

(3) To a solution of ethyl 4-butoxy-2-cyclopropylmethyl-6-fluoro-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (9.03 g, 25 mmol) in tetrahydrofuran (30 mL) and ethanol (30 mL) was added sodium hydroxide (3.00 g, 75 mmol). The obtained mixture was refluxed under heating for 12 h. The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in benzyl alcohol (20 mL) and the obtained solution was added dropwise to a solution of sodium hydride (5.0 g, 125 mmol) (60% in oil) in benzyl alcohol (20 mL). The obtained mixture was stirred at 150°C for 12 h. The reaction mixture was poured into 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from tetrahydrofuran - diisopropyl ether to give 6-benzyloxy-4-butoxy-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (7.31 g, 69.4%) as crystals. Melting point 178-179°C.

Elemental analysis for C₂₅H₂₇NO₅
Calculated: C, 71.24; H, 6.46; N, 3.32.

Found: C, 71.21; H, 6.68; N, 3.23.

¹H-NMR(CDCl₃) δ: 0.41-0.52 (4H, m), 0.97 (3H, t, J=7.4 Hz), 1.18-1.32 (1H, m), 1.38-1.57 (2H, m), 1.67-1.80 (2H, m), 3.88 (2H, t, J=6.4 Hz), 4.00 (2H, d, J=7.0 Hz), 5.17

⁵ (2H, s), 6.55 (1H, bs), 6.98 (1H, d, J=2.5 Hz), 7.16 (1H, dd, J=2.5, 8.8 Hz), 7.30-7.44 (5H, m), 8.25 (1H, d, J=8.8 Hz).

(4) To a solution of 6-benzyloxy-4-butoxy-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-

¹⁰ isoquinolinecarboxylic acid (7.16 g, 17 mmol) in tetrahydrofuran (50 mL) were added oxalyl chloride (1.8 mL, 20.4 mmol) and N,N-dimethylformamide (3 drops), and the mixture was stirred at room temperature for 1 h.

The reaction mixture was concentrated under reduced

¹⁵ pressure, and the residue was dissolved in tetrahydrofuran (30 mL). The obtained solution was added dropwise to a suspension of sodium tetrahydroborate (2.25 g, 59.5 mmol) in 1,2-dimethoxyethane (50 mL) at 0°C. The obtained mixture was

²⁰ stirred at 0°C for 1 h. The reaction mixture was poured into 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were

²⁵ recrystallized from ethyl acetate - n-hexane to give 6-benzyloxy-4-butoxy-2-cyclopropylmethyl-3-hydroxymethyl-1(2H)-isoquinolinone (1.72 g, 57.1%) as crystals.

Melting point 96-97°C.

Elemental analysis for C₂₅H₂₉NO₄

³⁰ Calculated: C, 73.68; H, 7.17; N, 3.44.

Found: C, 73.53; H, 7.10; N, 3.39.

¹H-NMR(CDCl₃) δ: 0.45-0.55 (4H, m), 1.02 (3H, t, J=7.3 Hz), 1.12-1.24 (1H, m), 1.44-1.62 (2H, m), 1.72-1.86 (2H, m), 3.79 (2H, t, J=6.6 Hz), 4.17 (2H, d, J=6.4 Hz), 4.82

³⁵ (2H, d, J=5.2 Hz), 5.19 (2H, s), 7.05 (1H, d, J=2.6 Hz), 7.11 (1H, dd, J=2.6, 8.8 Hz), 7.31-7.48 (5H, m), 8.28

(1H, d, J=8.8 Hz).

(5) To a suspension of 6-benzyloxy-4-butoxy-2-cyclopropylmethyl-3-hydroxymethyl-1(2H)-isoquinolinone (6.11 g, 15 mmol) in toluene (50 mL) was added thionyl chloride (2.2 mL, 30 mmol). The obtained mixture was refluxed under heating for 2 h. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 6-benzyloxy-4-butoxy-3-chloromethyl-2-cyclopropylmethyl-1(2H)-isoquinolinone (6.17 g, 96.7%) as crystals.

¹H-NMR(CDCl₃) δ: 0.47-0.55 (4H, m), 1.03 (3H, t, J=7.5 Hz), 1.06-1.18 (1H, m), 1.48-1.63 (2H, m), 1.79-1.86 (2H, m), 3.90 (2H, t, J=6.6 Hz), 4.20 (2H, d, J=6.6 Hz), 4.84 (2H, s), 5.22 (2H, s), 7.14-7.26 (2H, m), 7.34-7.47 (5H, m), 8.36 (1H, d, J=9.0 Hz).

(6) A solution of 6-benzyloxy-4-butoxy-3-chloromethyl-2-cyclopropylmethyl-1(2H)-isoquinolinone (5.96 g, 14 mmol) and potassium phthalimide (3.89 g, 21 mmol) in N,N-dimethylformamide (50 mL) was stirred at room temperature for 6 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give 2-[(6-benzyloxy-4-butoxy-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl]-1H-isoindole-1,3(2H)-dione (7.14 g, 95.1%) as crystals.

Melting point 127-128°C.

Elemental analysis for C₃₃H₃₂N₂O₅

Calculated: C, 73.86; H, 6.01; N, 5.22.

35 Found: C, 73.73; H, 5.79; N, 5.22.

¹H-NMR(CDCl₃) δ: 0.43-0.48 (4H, m), 0.97 (3H, t, J=7.3

Hz), 1.01-1.04 (1H, m), 1.37-1.55 (2H, m), 1.71-1.86 (2H, m), 3.89 (2H, t, J=6.8 Hz), 4.15 (2H, d, J=6.2 Hz), 5.06 (2H, s), 5.20 (2H, s), 7.12-7.17 (2H, m), 7.30-7.46 (5H, m), 7.70-7.86 (4H, m), 8.32-8.38 (1H, m).

5 (7) To a solution of 2-[(6-benzyloxy-4-butoxy-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl]-1H-isoindole-1,3(2H)-dione (6.97 g, 13 mmol) in ethanol (50 mL) was added hydrazine monohydrate (1.9 mL, 39 mmol). The obtained mixture was
10 refluxed under heating for 2 h. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under
15 reduced pressure. The residue was dissolved in tetrahydrofuran (50 mL) and di-t-butyl dicarbonate (4.5 mL, 19.5 mmol) was added thereto. The obtained mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate.
20 The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - n-hexane to give
25 tert-butyl (6-benzyloxy-4-butoxy-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (6.34 g, 96.4%) as crystals.

Melting point 106-107°C.

Elemental analysis for C₃₀H₃₈N₂O₅ 0.25H₂O

Calculated: C, 70.50; H, 7.59; N, 5.48.

30 Found: C, 70.61; H, 7.48; N, 5.45.

¹H-NMR(CDCl₃) δ: 0.49-0.52 (4H, m), 1.02 (3H, t, J=7.3 Hz), 1.15-1.26 (1H, m), 1.46 (9H, s), 1.51-1.62 (2H, m), 1.72-1.87 (2H, m), 3.77 (2H, t, J=6.5 Hz), 4.08 (2H, d, J=5.6 Hz), 4.51 (2H, d, J=5.6 Hz), 4.79 (1H, bs), 5.21 (2H, s), 7.07 (1H, d, J=2.6 Hz), 7.14 (1H, dd, J=2.6, 8.8 Hz), 7.33-7.49 (5H, m), 8.34 (1H, d, J=8.8 Hz).

- (8) A suspension of tert-butyl (6-benzyloxy-4-butoxy-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isoquinolinyl)-methylcarbamate (6.08 g, 12 mmol) and 5% palladium carbon (2.0 g) in tetrahydrofuran (30 mL) and ethanol (30 mL) was stirred under a hydrogen atmosphere at room temperature for 2 h. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The obtained crystals were recrystallized from tetrahydrofuran - diisopropyl ether to give tert-butyl (4-butoxy-2-cyclopropylmethyl-6-hydroxy-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (4.87 g, 97.6%) as crystals.
- Melting point 164-166°C.
- Elemental analysis for C₂₃H₃₂N₂O₅
- Calculated: C, 66.32; H, 7.74; N, 6.73.
Found: C, 66.16; H, 7.69; N, 6.82.
¹H-NMR(CDCl₃) δ: 0.48-0.52 (4H, m), 0.96 (3H, t, J=7.4 Hz), 1.13-1.26 (1H, m), 1.45-1.58 (11H, m), 1.69-1.84 (2H, m), 3.83 (2H, t, J=6.2 Hz), 4.12 (2H, d, J=6.6 Hz), 4.53 (2H, d, J=5.2 Hz), 4.89 (1H, bs), 7.06-7.12 (2H, m), 8.25 (1H, d, J=8.4 Hz), 9.24 (1H, bs).
- (9) A solution of tert-butyl (4-butoxy-2-cyclopropylmethyl-6-hydroxy-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.42 g, 1 mmol), 2-iodoacetamide (0.27 g, 1.5 mmol) and 1,8-diazabicyclo[5.4.0]-7-undecene (0.22 mL, 1.5 mmol) in N,N-dimethylformamide (10 mL) was stirred at 80°C for 10 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [6-(2-amino-2-oxoethoxy)-4-butoxy-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isoquinolinyl]-methylcarbamate (0.36 g, 76.6%) as crystals.
- Melting point 209-210°C.

Elemental analysis for C₂₅H₃₅N₃O₆

Calculated: C, 63.41; H, 7.45; N, 8.87.

Found: C, 63.05; H, 7.31; N, 8.61.

¹H-NMR(CDCl₃) δ: 0.48-0.56 (4H, m), 1.04 (3H, t, J=7.2 Hz), 1.15-1.26 (1H, m), 1.46 (9H, s), 1.48-1.69 (2H, m), 1.80-1.91 (2H, m), 3.86 (2H, t, J=6.4 Hz), 4.09 (2H, d, J=6.6 Hz), 4.53 (2H, d, J=5.6 Hz), 4.62 (2H, s), 4.86 (1H, bs), 5.89 (1H, bs), 6.62 (1H, bs), 7.06-7.12 (2H, m), 8.36 (1H, d, J=9.2 Hz).

(10) To a solution of tert-butyl [6-(2-amino-2-oxoethoxy)-4-butoxy-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.28 g, 0.6 mmol) in ethyl acetate (5 mL) was added a solution of 4N hydrogen chloride in ethyl acetate (5 mL) and the obtained solution was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the precipitated crystals were recrystallized from methanol - diisopropyl ether to give 2-[[3-(aminomethyl)-4-butoxy-2-cyclopropylmethyl-1-oxo-1,2-dihydro-6-isooquinolinyl]oxy]acetamide hydrochloride (0.23 g, 92.0%) as crystals.

Melting point 133-134°C.

Elemental analysis for C₂₀H₂₈N₃O₄Cl 1.5H₂O

Calculated: C, 54.98; H, 7.15; N, 9.62.

Found: C, 54.84; H, 6.90; N, 9.54.

¹H-NMR(DMSO-d₆) δ: 0.43-0.46 (4H, m), 1.00 (3H, t, J=7.1 Hz), 1.12-1.21 (1H, m), 1.50-1.63 (2H, m), 1.81-1.92 (2H, m), 3.93 (2H, t, J=6.1 Hz), 4.04 (2H, d, J=6.2 Hz), 4.18 (2H, s), 4.64 (2H, s), 7.23 (1H, d, J=8.8 Hz), 7.47 (1H, s), 7.75 (1H, s), 8.21 (1H, d, J=8.8 Hz), 8.68 (3H, s).

Example 150

2-[[3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isooquinolinyl]oxy]acetamide hydrochloride
 (1) A solution of 4-fluorophthalic anhydride (24.99 g, 150 mmol) and ethyl 2-(isobutylamino)acetate (23.88 g, 150 mmol) in tetrahydrofuran (200 mL) was stirred at

room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in N,N-dimethylformamide (200 mL), and potassium carbonate (20.73 g, 150 mmol) and ethyl iodide (14.4 mL, 180 mmol) were added thereto. The mixture was stirred at room temperature for 3 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in ethanol (300 mL) and a solution of 20% sodium ethoxide ethanol solution (102 g, 300 mmol) was added thereto. The mixture was stirred at room temperature for 1 h. The reaction mixture was poured into 1N hydrochloric acid (300 mL) and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography and the component eluted earlier was concentrated to give ethyl 7-fluoro-4-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (19.2 g, 41.7%) as crystals.

Melting point 104-105°C.

Elemental analysis for C₁₆H₁₆NO₄F

Calculated: C, 62.53; H, 5.90; N, 4.56.

Found: C, 62.81; H, 5.99; N, 4.67.

¹H-NMR(CDCl₃) δ: 0.82 (6H, d, J=6.6 Hz), 1.46 (3H, t, J=7.2 Hz), 1.76-1.89 (1H, m), 4.41 (2H, d, J=7.2 Hz), 4.49 (2H, d, J=7.2 Hz), 7.43-7.50 (1H, m), 8.08-8.21 (2H, m), 11.34 (1H, s).

The component eluted later was concentrated to give ethyl 6-fluoro-4-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (13.41 g, 29.1%) as crystals.

Melting point 91-92°C.

Elemental analysis for C₁₆H₁₈NO₄F

Calculated: C, 62.53; H, 5.90; N, 4.56.

Found: C, 62.73; H, 5.83; N, 4.53.

5 ¹H-NMR(CDCl₃) δ: 0.82 (6H, d, J=6.6 Hz), 1.46 (3H, t, J=7.2 Hz), 1.74-1.86 (1H, m), 4.40 (2H, d, J=7.5 Hz), 4.49 (2H, d, J=7.2 Hz), 7.34-7.42 (1H, m), 7.75-7.80 (1H, m), 8.45-8.51 (1H, m), 11.12 (1H, s).

(2) To a solution of ethyl 6-fluoro-4-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (9.22 g, 30 mmol), 1-butanol (3.3 mL, 45 mmol) and tributylphosphine (14.9 mL, 60 mmol) in tetrahydrofuran (100 mL) was added 1,1'-(azodicarbonyl)dipiperidine (15.14 g, 60 mmol) and the mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography to give ethyl 4-butoxy-6-fluoro-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (9.25 g, 84.9%) as an oil.

20 ¹H-NMR(CDCl₃) δ: 0.91 (6H, d, J=6.6 Hz), 1.01 (3H, t, J=7.4 Hz), 1.45 (3H, t, J=7.2 Hz), 1.46-1.66 (2H, m), 1.74-1.84 (2H, m), 2.05-2.18 (1H, m), 3.88 (2H, d, J=7.8 Hz), 3.95 (2H, t, J=6.6 Hz), 4.46 (2H, q, J=7.2 Hz), 7.27-7.29 (1H, m), 7.34-7.38 (1H, m), 8.44-8.48 (1H, m).

25 (3) To a solution of ethyl 4-butoxy-6-fluoro-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (9.09 g, 25 mmol) in tetrahydrofuran (30 mL) and ethanol (30 mL) was added sodium hydroxide (3.00 g, 75 mmol). The obtained mixture was refluxed under heating for 12 h. The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in benzyl alcohol (20 mL) and the obtained solution was added dropwise to a solution of sodium hydride (5.0 g, 125 mmol)(60% in

oil) in benzyl alcohol (20 mL). The obtained mixture was stirred at 150°C for 12 h. The reaction mixture was poured into 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from tetrahydrofuran - diisopropyl ether to give 6-benzyloxy-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (9.32 g, 88.1%) as crystals.

Melting point 151-152°C.

Elemental analysis for C₂₅H₂₉NO₅

Calculated: C, 70.90; H, 6.90; N, 3.31.

Found: C, 70.89; H, 6.91; N, 3.37.

¹⁵ ¹H-NMR(CDCl₃) δ: 0.85 (6H, d, J=7.0 Hz), 0.98 (3H, t, J=7.3 Hz), 1.39-1.58 (2H, m), 1.67-1.81 (2H, m), 2.06-2.19 (1H, m), 3.89 (2H, t, J=6.6 Hz), 3.95 (2H, d, J=7.8 Hz), 5.16 (2H, s), 6.96 (1H, d, J=2.6 Hz), 7.17 (1H, dd, J=2.6, 9.0 Hz), 7.32-7.45 (5H, m), 8.23 (1H, d, J=9.0 Hz).

²⁰ (4) To a solution of 6-benzyloxy-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (7.62 g, 18 mmol) in tetrahydrofuran (50 mL) were added oxalyl chloride (1.9 mL, 21.6 mmol) and N,N-dimethylformamide (2 drops), and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in tetrahydrofuran (30 mL). The obtained solution was added dropwise to a suspension of sodium ²⁵ tetrahydorboration (2.38 g, 63 mmol) in 1,2-dimethoxyethane (50 mL) at 0°C. The obtained mixture was stirred at 0°C for 1 h. The reaction mixture was poured into 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were

recrystallized from ethyl acetate - diisopropyl ether to give 6-benzyloxy-4-butoxy-3-hydroxymethyl-2-isobutyl-1(2H)-isoquinolinone (7.11 g, 96.5%) as crystals.
Melting point 90-91°C.

5 Elemental analysis for C₂₅H₃₁NO₄0.25H₂O

Calculated: C, 72.53; H, 7.67; N, 3.38.

Found: C, 72.86; H, 7.71; N, 3.31.

¹H-NMR(CDCl₃) δ: 0.92 (6H, d, J=6.6 Hz), 1.02 (3H, t, J=7.1 Hz), 1.48-1.60 (2H, m), 1.72-1.85 (2H, m), 2.11-10 2.25 (1H, m), 2.44 (1H, bs), 3.79 (2H, t, J=6.4 Hz), 4.05 (2H, d, J=7.4 Hz), 4.79 (2H, d, J=5.4 Hz), 5.19 (2H, s), 7.06-7.13 (2H, m), 7.34-7.45 (4H, m), 8.28 (1H, d, J=8.4 Hz).

(5) To a suspension of 6-benzyloxy-4-butoxy-3-

15 hydroxymethyl-2-isobutyl-1(2H)-isoquinolinone (6.96 g, 17 mmol) in toluene (50 mL) was added thionyl chloride (2.5 mL, 34 mmol). The obtained mixture was refluxed under heating for 2 h. The reaction mixture was poured into saturated aqueous sodium hydrogen carbonate solution 20 and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 6-benzyloxy-4-butoxy-3-chloromethyl-2-isobutyl-1(2H)-isoquinolinone (6.90 g, 94.8%) as crystals.

25 ¹H-NMR(CDCl₃) δ: 0.95 (6H, d, J=7.0 Hz), 1.03 (3H, t, J=7.3 Hz), 1.47-1.65 (2H, m), 1.76-1.90 (2H, m), 2.09-2.23 (1H, m), 3.88 (2H, t, J=6.4 Hz), 4.05 (2H, d, J=7.2 Hz), 4.80 (2H, s), 5.21 (2H, s), 7.13-7.47 (7H, m), 8.36 (1H, d, J=8.8 Hz).

30 (6) A solution of 6-benzyloxy-4-butoxy-3-chloromethyl-2-isobutyl-1(2H)-isoquinolinone (6.85 g, 16 mmol) and potassium phthalimide (4.44 g, 24 mmol) in N,N-dimethylformamide (50 mL) was stirred at room temperature for 6 h. The reaction mixture was poured

35 into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried

over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 2-[(6-benzyloxy-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-

5 isoquinolinyl)methyl]-1H-isoindole-1,3(2H)-dione (7.08 g, 82.2%) as an amorphous.

¹H-NMR(CDCl₃) δ: 0.93-1.01 (9H, m), 1.41-1.55 (2H, m), 1.71-1.85 (2H, m), 2.05-2.22 (1H, m), 3.89 (2H, t, J=6.9 Hz), 4.01 (2H, d, J=7.2 Hz), 5.01 (2H, s), 5.20 (2H, s),

10 7.13-7.17 (2H, m), 7.30-7.46 (5H, m), 7.68-7.87 (2H, m), 8.32-8.36 (1H, m).

(7) To a solution of 2-[(6-benzyloxy-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl]-1H-isoindole-1,3(2H)-dione (7.00 g, 13 mmol) in ethanol (50

15 mL) was added hydrazine monohydrate (1.9 mL, 39 mmol). The obtained mixture was refluxed under heating for 2 h. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried

20 over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (50 mL) and di-t-butyl dicarbonate (4.5 mL, 19.5 mmol) was added thereto. The obtained mixture was stirred at room temperature for 1 h. The reaction

25 mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - n-hexane to give

30 tert-butyl (6-benzyloxy-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (6.44 g, 97.4%) as crystals.

Melting point 104-105°C.

Elemental analysis for C₃₀H₄₀N₂O₅

35 Calculated: C, 70.84; H, 7.93; N, 5.51.

Found: C, 70.85; H, 7.70; N, 5.48.

¹H-NMR(CDCl₃) δ: 0.94 (6H, d, J=7.0 Hz), 1.02 (3H, t, J=7.3 Hz), 1.46-1.62 (11H, m), 1.72-1.86 (2H, m), 2.05-2.22 (1H, m), 3.75 (2H, t, J=6.6 Hz), 3.96 (2H, d, J=7.6 Hz), 4.48 (2H, d, J=5.4 Hz), 4.73 (1H, bs), 5.21 (2H, s), 7.08 (1H, d, J=2.6 Hz), 7.15 (1H, dd, J=2.6, 8.8 Hz), 7.30-7.47 (5H, m), 8.34 (1H, d, J=8.8 Hz).

(8) A suspension of tert-butyl (6-benzyloxy-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (6.10 g, 12 mmol) and 5% palladium carbon (2.0 g) in tetrahydrofuran (30 mL) and ethanol (30 mL) was stirred under a hydrogen atmosphere at room temperature for 2 h. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give tert-butyl (4-butoxy-6-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (4.86 g, 96.8%) as crystals.

Melting point 185-186°C.

(20) Elemental analysis for C₂₃H₃₄N₂O₅

Calculated: C, 66.00; H, 8.19; N, 6.69.
Found: C, 66.02; H, 8.14; N, 6.73.

¹H-NMR(CDCl₃) δ: 0.95 (6H, d, J=6.6 Hz), 0.96 (3H, t, J=7.0 Hz), 1.46-1.58 (11H, m), 1.72-1.85 (2H, m), 2.06-2.25 (1H, m), 3.82 (2H, t, J=6.6 Hz), 4.00 (2H, d, J=6.8 Hz), 4.51 (2H, d, J=4.8 Hz), 4.84 (1H, bs), 7.09-7.13 (2H, m), 8.27 (1H, d, J=9.6 Hz), 8.98 (1H, bs).

(9) A solution of tert-butyl (4-butoxy-6-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.42 g, 1 mmol), 2-iodoacetamide (0.27 g, 1.5 mmol) and 1,8-diazabicyclo[5.4.0]-7-undecene (0.22 mL, 1.5 mmol) in N,N-dimethylformamide (10 mL) was stirred at 80°C for 10 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and

concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give tert-butyl [6-(2-amino-2-oxoethoxy)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-

⁵ isoquinolinyl]methylcarbamate (0.37 g, 78.7%) as crystals.

Melting point 180-181°C.

Elemental analysis for C₂₅H₃₇N₃O₆

Calculated: C, 63.14; H, 7.84; N, 8.84.

¹⁰ Found: C, 62.90; H, 7.71; N, 8.98.

¹H-NMR(CDCl₃) δ: 0.95 (6H, d, J=6.6 Hz), 1.04 (3H, t, J=7.3 Hz), 1.46 (9H, s), 1.51-1.67 (2H, m), 1.80-1.94 (2H, m), 2.05-2.23 (2H, m), 3.84 (2H, t, J=6.6 Hz), 3.98 (2H, d, J=7.2 Hz), 4.51 (2H, d, J=5.6 Hz), 4.62 (2H, s),
¹⁵ 4.76 (1H, bs), 5.84 (1H, bs), 6.59 (1H, bs), 7.07-7.13 (2H, m), 8.37 (1H, d, J=9.2 Hz).

(10) To a solution of tert-butyl [6-(2-amino-2-oxoethoxy)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.29 g, 0.6 mmol) in

²⁰ ethyl acetate (5 mL) was added a solution of 4N hydrogen chloride in ethyl acetate (5 mL) and the obtained solution was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the precipitated crystals were recrystallized from

²⁵ methanol - diisopropyl ether to give 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]oxy]acetamide hydrochloride (0.23 g, 92.0%) as crystals.

Melting point 248-250°C.

³⁰ Elemental analysis for C₂₀H₃₀N₃O₄Cl 0.5H₂O

Calculated: C, 57.07; H, 7.42; N, 9.98.

Found: C, 57.22; H, 7.67; N, 9.73.

¹H-NMR(DMSO-d₆) δ: 0.87 (6H, d, J=6.6 Hz), 0.99 (3H, t, J=7.3 Hz), 1.47 (9H, s), 1.47-1.65 (2H, m), 1.73-2.04

³⁵ (3H, m), 3.88-3.95 (4H, m), 4.17 (2H, s), 4.64 (2H, s), 7.06 (1H, d, J=2.5 Hz), 7.23 (1H, dd, J=2.5, 8.8 Hz),

7.46 (1H, s), 7.73 (1H, s), 8.20 (1H, d, J=9.2 Hz), 8.62 (3H, s).

Example 151

(E)-3-[3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenamide hydrochloride

5 (1) To a solution of ethyl diethylphosphonoacetate (1.4 mL, 7 mmol) in N,N-dimethylformamide (30 mL) was added sodium hydride (0.28 g, 7 mmol) (60% in oil) and the mixture was stirred at room temperature for 10 min. To 10 the obtained mixture was added a solution of tert-butyl (4-butoxy-6-formyl-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (3.01 g, 7 mmol) in N,N-dimethylformamide (10 mL) and the mixture was stirred at room temperature for 1 h. The reaction mixture was 15 poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give ethyl (E)-3-(4-butoxy-3-[(tert- 20 butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl)-2-propenate (3.11 g, 88.9%) as crystals.

¹H-NMR(CDCl₃). δ: 0.96 (6H, d, J=6.6 Hz), 1.06 (3H, t, J=7.2 Hz), 1.37 (3H, t, J=7.2 Hz), 1.47 (9H, s), 1.53- 25 1.68 (2H, m), 1.84-1.94 (2H, m), 2.12-2.22 (1H, m), 3.87 (2H, t, J=6.6 Hz), 3.99 (2H, d, J=7.5 Hz), 4.30 (2H, q, J=7.2 Hz), 4.52 (2H, d, J=5.7 Hz), 4.78 (1H, bs), 6.58 (1H, d, J=16.0 Hz), 7.65 (1H, dd, J=1.5, 8.1 Hz), 7.79 (1H, d, J=1.5 Hz), 7.79 (1H, d, J=16.0 Hz), 8.41 (1H, d, 30 J=8.1 Hz).

(2) To a solution of ethyl (E)-3-(4-butoxy-3-[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl)-2-propenate (1.00 g, 2 mmol) in tetrahydrofuran (10 mL) and ethanol (10 mL) was added 1N 35 sodium hydroxide (4 mL). The obtained mixture was stirred at room temperature for 2 h. The reaction

mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give (E)-3-(4-butoxy-3-[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl)-2-propenic acid (0.89 g, 94.7%) as crystals.

10 Melting point 207-209°C.

Elemental analysis for C₂₆H₃₆N₂O₆

Calculated: C, 66.08; H, 7.68; N, 5.93.

Found: C, 65.85; H, 7.52; N, 5.91.

¹H-NMR(CDCl₃) δ: 0.96 (6H, d, J=6.6 Hz), 1.07 (3H, t, J=7.3 Hz), 1.49 (9H, s), 1.49-1.69 (2H, m), 1.83-1.97 (2H, m), 2.05-2.24 (1H, m), 3.88 (2H, t, J=6.4 Hz), 3.99 (2H, d, J=7.2 Hz), 4.53 (2H, d, J=5.6 Hz), 5.16 (1H, bs), 6.58 (1H, d, J=16.0 Hz), 7.62 (1H, d, J=8.2 Hz), 7.71 (1H, s), 7.84 (1H, d, J=16.0 Hz), 8.36 (1H, d, J=8.2 Hz).

15 (3) A solution of (E)-3-(4-butoxy-3-[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)-2-propenic acid (0.47 g, 1 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.38 g, 2 mmol) and 1-

20 hydroxybenzotriazole ammonium salt (0.30 g, 2 mmol) in N,N-dimethylformamide (10 mL) was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous

25 magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - n-hexane to give (E)-3-(4-butoxy-3-[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)-2-propenamide (0.41 g, 87.2%) as crystals.

30 Melting point 149-150°C.

Elemental analysis for $C_{26}H_{37}N_3O_5$ 0.5H₂O

Calculated: C, 64.98; H, 7.97; N, 8.74.

Found: C, 64.71; H, 7.68; N, 8.56.

¹H-NMR(CDCl₃) δ: 0.96 (6H, d, J=6.6 Hz), 1.01 (3H, t,

⁵ J=7.4 Hz), 1.47 (9H, s), 1.49-1.67 (2H, m), 1.81-1.95 (2H, m), 2.09-2.21 (1H, m), 3.86 (2H, t, J=6.5 Hz), 3.99 (2H, d, J=7.2 Hz), 4.52 (2H, d, J=5.6 Hz), 4.95 (1H, bs), 5.86 (1H, bs), 6.01 (1H, bs), 6.60 (1H, d, J=16.2 Hz), 7.58 (1H, d, J=8.5 Hz), 7.71 (1H, s), 7.74 (1H, d,

¹⁰ J=16.2 Hz), 8.33 (1H, d, J=8.4 Hz).

(4) To a solution of (E)-3-(4-butoxy-3-[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)-2-propenamide (0.14 g, 0.3 mmol) in ethyl acetate (5 mL) was added a solution of 4N

¹⁵ hydrogen chloride in ethyl acetate (5 mL) and the obtained solution was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the precipitated crystals were recrystallized from methanol - diisopropyl ether to give

²⁰ (E)-3-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenamide hydrochloride (0.11 g, 91.7%) as crystals.

Melting point 223-225°C.

Elemental analysis for $C_{21}H_{30}N_3O_3Cl$ 0.5H₂O

²⁵ Calculated: C, 60.49; H, 7.49; N, 10.08.

Found: C, 60.37; H, 7.77; N, 9.73.

¹H-NMR(DMSO-d₆) δ: 0.89 (6H, d, J=6.6 Hz), 1.01 (3H, t, J=7.2 Hz), 1.48-1.66 (2H, m), 1.82-2.08 (3H, m), 3.93-3.99 (4H, m), 4.18 (2H, d, J=4.8 Hz), 6.84 (1H, d,

³⁰ J=16.1 Hz), 7.28 (1H, bs), 7.64 (1H, d, J=16.1 Hz), 7.76 (1H, bs), 7.80-7.87 (2H, m), 8.29 (1H, d, J=8.0 Hz), 8.64 (3H, bs).

Example 152

(E)-3-[3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-

³⁵ dihydro-6-isoquinolinyl]-2-propenamide

(1) To a suspension of (E)-3-[3-(aminomethyl)-4-butoxy-

2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenamide hydrochloride (2.04 g, 5 mmol) in water (20 mL) was added 1N sodium hydroxide (20 mL). The obtained mixture was stirred at room temperature for 10 min. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate to give (E)-3-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenamide (1.02 g, 85.0%) as crystals. Melting point 173-175°C.

Elemental analysis for $C_{21}H_{29}N_3O_3$

Calculated: C, 67.90; H, 7.87; N, 11.31.

Found: C, 67.73; H, 7.90; N, 11.03.

1H -NMR($CDCl_3$) δ : 0.96 (6H, d, $J=6.6$ Hz), 1.05 (3H, t, $J=7.3$ Hz), 1.42 (2H, bs), 1.47-1.69 (2H, m), 1.81-1.95 (1H, m), 3.89 (2H, t, $J=6.4$ Hz), 4.01 (2H, s), 4.10 (2H, d, $J=7.4$ Hz), 5.89 (1H, bs), 6.04 (1H, bs), 6.65 (1H, d, $J=15.6$ Hz), 7.62 (1H, dd, $J=1.4, 8.4$ Hz), 7.76 (1H, d, $J=1.4$ Hz), 7.78 (1H, d, $J=15.6$ Hz), 8.39 (1H, d, $J=8.4$ Hz).

Powder X-ray crystal diffraction data.

Diffraction angle: $2\theta(^{\circ})$ spacing: d value

(angstrom)

	8.62	10.2
	9.98	8.86
	17.4	5.09
	23.0	3.87
30	21.9	4.06
	26.3	3.38
	24.2	3.68

Example 153

3-(Aminomethyl)-4-butoxy-2-isobutyl-6-(1,3-oxazol-5-yl)-

35 1(2H)-isoquinolinone hydrochloride

(1) A solution of tert-butyl (4-butoxy-6-formyl-2-

isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.34 g, 0.8 mmol), p-toluenesulfonylmethyl isocyanide (0.16 g, 0.8 mmol) and potassium carbonate (0.22 g, 1.6 mmol) in methanol (10 mL) was refluxed under heating for 30 min. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography and the precipitated crystals were recrystallized from ethyl acetate - diisopropyl ether to give tert-butyl [4-butoxy-2-isobutyl-6-(1,3-oxazol-5-yl)-1-oxo-1,2-dihydro-3-isoquinolinyl]-methylcarbamate (0.34 g, 91.9%) as crystals.

Melting point 152-153°C.

Elemental analysis for $C_{26}H_{35}N_3O_5$

Calculated: C, 66.50; H, 7.51; N, 8.95.

Found: C, 66.25; H, 7.57; N, 9.00.

1H -NMR($CDCl_3$) δ : 0.97 (6H, d, $J=7.0$ Hz), 1.07 (3H, t, $J=7.3$ Hz), 1.47 (9H, s), 1.55-1.73 (2H, m), 1.84-1.98 (2H, m), 2.12-2.26 (1H, m), 3.91 (2H, t, $J=6.4$ Hz), 4.00 (2H, d, $J=7.4$ Hz), 4.54 (2H, d, $J=5.4$ Hz), 4.81 (1H, bs), 7.53 (1H, d, $J=0.8$ Hz), 7.72-7.78 (1H, m), 7.97 (1H, s), 8.01 (1H, d, $J=0.8$ Hz), 8.45 (1H, dd, $J=1.4$, 8.4 Hz).

(2) To a solution of tert-butyl [4-butoxy-2-isobutyl-6-(1,3-oxazol-5-yl)-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.28 g, 0.6 mmol) in ethyl acetate (5 mL) was added a solution of 4N hydrogen chloride in ethyl acetate (5 mL) and the obtained solution was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the precipitated crystals were recrystallized from methanol - diisopropyl ether to give 3-(aminomethyl)-4-butoxy-2-isobutyl-6-(1,3-oxazol-5-yl)-1(2H)-isoquinolinone hydrochloride (0.22 g, 91.7%) as crystals.

Melting point 211-213°C.

¹H-NMR(DMSO-d₆) δ: 0.90 (6H, d, J=6.6 Hz), 1.03 (3H, t, J=7.3 Hz), 1.55-1.67 (2H, m), 1.84-1.93 (2H, m), 2.02-2.12 (1H, m), 3.96-4.01 (4H, m), 4.20 (2H, d, J=5.4 Hz), 8.00-8.02 (3H, m), 8.36 (1H, d, J=9.0 Hz), 8.64 (1H, s),
5 8.82 (3H, bs).

Example 154

2-[[3-(Aminomethyl)-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]oxy]acetamide

(1) To a suspension of 4-benzyloxyphthalic anhydride

10 (25.42 g, 100 mmol) in methanol (200 mL) was added 28% sodium methoxide methanol solution (21.22 g, 110 mmol) and the mixture was stirred at room temperature for 1 h.

The reaction mixture was poured into 1N hydrochloric acid (150 mL) and extracted with ethyl acetate. The

15 extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in N,N-dimethylformamide (200 mL) and methyl 2-

(isobutylamino)acetate (17.42 g, 120 mmol), 1-ethyl-3-

20 (3-dimethylaminopropyl)carbodiimide hydrochloride (23.00 g, 120 mmol) and 1-hydroxybenzotriazole (18.34 g, 120 mmol) were added, and the mixture was stirred at room temperature for 3 h. The reaction mixture was poured into water and extracted with ethyl acetate. The

25 extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in methanol (50 mL) and a solution of 28% sodium methoxide methanol solution (38.59 g, 200 mmol) was added thereto. The mixture was

30 stirred at room temperature for 1 h. The reaction mixture was poured into 1N hydrochloric acid (200 mL) and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The

35 residue was purified by silica gel column chromatography and the component eluted earlier was concentrated to

give methyl 7-benzyloxy-4-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (4.76 g, 12.1%) as an oil.

¹H-NMR(CDCl₃) δ: 0.82 (6H, d, J=6.6 Hz), 1.78-1.87 (1H, m), 3.99 (3H, s), 4.39 (2H, d, J=7.5 Hz), 5.25 (2H, s), 7.25-7.48 (6H, m), 7.96-7.98 (1H, m), 8.10 (1H, d, J=8.7 Hz), 11.34 (1H, s).

The component eluted later was concentrated to give methyl 6-benzyloxy-4-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (21.41 g, 54.4%) as crystals.

Melting point 109-110°C.

Elemental analysis for C₂₂H₂₃NO₅

Calculated: C, 69.28; H, 6.08; N, 3.67.

Found: C, 69.28; H, 5.93; N, 3.48.

¹H-NMR(CDCl₃) δ: 0.81 (6H, d, J=6.6 Hz), 1.66-1.85 (1H, m), 4.00 (3H, s), 4.35 (2H, d, J=7.5 Hz), 5.21 (2H, s), 7.31 (1H, dd, J=2.6, 8.8 Hz), 7.38-7.49 (5H, m), 7.60 (1H, d, J=2.6 Hz), 8.38 (1H, d, J=8.8 Hz), 11.12 (1H, s).

(2) To a solution of methyl 6-benzyloxy-4-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (7.86 g, 20 mmol) in N,N-dimethylformamide (100 mL) was added sodium hydride (0.96 g, 24 mmol) (60% in oil) at 0°C and the mixture was stirred at 0°C for 30 min. To

the obtained mixture was added N-phenyltrifluoromethanesulfonimide (8.57 g, 24 mmol) and the mixture was stirred at room temperature for 3 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with

water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give methyl 6-benzyloxy-2-isobutyl-1-oxo-4-trifluoromethanesulfonyloxy-1,2-dihydro-3-

isoquinolinecarboxylate (10.50 g, 100%) as an oil.

¹H-NMR(CDCl₃) δ: 0.88 (6H, d, J=7.0 Hz), 1.92-2.05 (1H,

m), 3.99 (3H, s), 5.19 (2H, s), 7.23-7.48 (2H, m), 8.37 (1H, d, J=9.2 Hz).

(3) A mixture of methyl 6-benzyloxy-2-isobutyl-1-oxo-4-trifluoromethanesulfonyloxy-1,2-dihydro-3-

5 isoquinolinecarboxylate (10.50 g, 20 mmol), 2-fluorophenylboronic acid (3.36 g, 24 mmol) and sodium carbonate (5.30 g, 50 mmol) in toluene (50 mL), ethanol (10 mL) and water (10 mL) was stirred under an argon atmosphere at room temperature for 30 min. To the

10 obtained mixture was added tetrakis(triphenylphosphine)palladium (1.16 g, 1 mmol) and the mixture was refluxed under heating under an argon atmosphere for 12 h. The reaction mixture was poured into water and extracted with ethyl acetate.

15 After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give methyl 6-benzyloxy-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-

20 dihydro-3-isoquinolinecarboxylate (6.06 g, 65.9%) as crystals.

Melting point 106-107°C.

Elemental analysis for C₂₈H₂₆NO₄F

Calculated: C, 73.19; H, 5.70; N, 3.05.

25 Found: C, 73.18; H, 5.83; N, 2.86.

¹H-NMR(CDCl₃) δ: 0.91 (3H, d, J=6.6 Hz), 0.92 (3H, d, J=7.0 Hz), 2.05-2.19 (1H, m), 3.47 (3H, s), 3.86 (1H, dd, J=7.6, 13.8 Hz), 4.08 (1H, dd, J=7.6, 13.8 Hz), 4.98 (2H, s), 6.50-6.52 (1H, m), 7.13-7.50 (10H, m), 8.43 (1H, d, J=8.8 Hz).

(4) To a solution of methyl 6-benzyloxy-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (0.46 g, 1 mmol) in methanol (30 mL) was added an aqueous solution (3 mL) of lithium

35 hydroxide monohydrate (0.42 g, 10 mmol). The obtained mixture was refluxed under heating for 12 h. The

reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give 6-benzyloxy-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (0.41 g, 93.2%) as crystals.

Melting point 178-179°C.

Elemental analysis for $C_{27}H_{24}NO_4F$ 0.25H₂O
Calculated: C, 72.07; H, 5.49; N, 3.11.
Found: C, 72.28; H, 5.20; N, 2.80.
¹H-NMR(CDCl₃) δ: 0.85 (6H, d, J=6.8 Hz), 2.09-2.23 (1H, m), 3.75-3.96 (2H, m), 4.38 (1H, bs), 4.98 (2H, s), 6.49-6.51 (1H, m), 7.10-7.48 (10H, m), 8.30 (1H, d, J=8.8 Hz).

(5). To a solution of 6-benzyloxy-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (4.90 g, 11 mmol) in tetrahydrofuran (50 mL) were added oxalyl chloride (1.1 mL, 13.2 mmol) and N,N-dimethylformamide (3 drops), and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in tetrahydrofuran (30 mL). The obtained solution was added dropwise to a suspension of sodium tetrahydroborate (1.46 g, 38.5 mmol) in 1,2-dimethoxyethane (30 mL) at 0°C. The obtained mixture was stirred at 0°C for 1 h. The reaction mixture was poured into 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give 6-benzyloxy-4-(2-fluorophenyl)-3-hydroxymethyl-2-isobutyl-1(2H)-isoquinolinone (4.38 g, 92.4%) as

crystals.

Melting point 191-192°C.

Elemental analysis for C₂₇H₂₆NO₃F 0.25H₂O

Calculated: C, 74.38; H, 6.13; N, 3.21.

⁵ Found: C, 74.52; H, 6.20; N, 3.16.

¹H-NMR(CDCl₃) δ: 0.87 (6H, d, J=6.6 Hz), 1.85 (1H, bs), 2.18-2.32 (1H, m), 4.08-4.29 (2H, m), 4.44 (2H, s), 4.94 (2H, s), 6.38 (1H, d, J=2.3 Hz), 7.09 (1H, dd, J=2.3, 8.6 Hz), 7.18-7.36 (7H, m), 7.43-7.54 (1H, m), 8.36 (1H,

¹⁰ d, J=8.6 Hz).

(6) To a suspension of 6-benzyloxy-4-(2-fluorophenyl)-3-hydroxymethyl-2-isobutyl-1(2H)-isoquinolinone (4.31 g, 10 mmol) in toluene (50 mL) was added thionyl chloride (1.5 mL, 20 mmol). The obtained mixture was refluxed

¹⁵ under heating for 2 h. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give

²⁰ 6-benzyloxy-3-chloromethyl-4-(2-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone (4.29 g, 95.3%) as crystals.

¹H-NMR(CDCl₃) δ: 0.98 (3H, d, J=6.6 Hz), 1.01 (3H, d, J=6.8 Hz), 2.15-2.26 (1H, m), 3.94 (1H, dd, J=7.9, 13.1

²⁵ Hz), 4.31 (1H, d, J=12.4 Hz), 4.35 (1H, dd, J=7.9, 13.1 Hz), 4.43 (1H, d, J=12.4 Hz), 4.95 (2H, s), 6.36-6.38 (1H, m), 7.12-7.35 (9H, m), 7.45-7.56 (1H, m), 8.41 (1H, d, J=8.8 Hz).

(7) A solution of 6-benzyloxy-3-chloromethyl-4-(2-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone (4.27 g, 9.5 mmol) and potassium phthalimide (2.65 g, 14.3 mmol) in N,N-dimethylformamide (100 mL) was stirred at room temperature for 6 h. The reaction mixture was poured into water and extracted with ethyl acetate. After ³⁵ washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under

reduced pressure. The residue was purified by silica gel column chromatography to give 2-[(6-benzyloxy-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl]-1H-isoindole-1,3(2H)-dione (5.07 g,
5 95.3%) as an amorphous.

¹H-NMR(CDCl₃) δ: 1.00 (3H, d, J=6.6 Hz), 1.01 (3H, d, J=6.8 Hz), 2.12-2.27 (1H, m), 3.94 (1H, dd, J=7.3, 14.8 Hz), 4.33 (1H, dd, J=7.3, 13.9 Hz), 4.57 (1H, d, J=15.6 Hz), 4.92 (1H, d, J=15.6 Hz), 4.93 (2H, s), 6.34 (1H, d, J=2.6 Hz), 7.01-7.45 (10H, m), 7.66-7.76 (4H, m), 8.40 (1H, d, J=8.8 Hz).

(8) To a solution of 2-[(6-benzyloxy-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl]-1H-isoindole-1,3(2H)-dione (5.05 g, 9 mmol) in ethanol (50 mL) was added hydrazine monohydrate (1.3 mL, 27 mmol). The obtained mixture was refluxed under heating for 2 h. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (50 mL) and di-t-butyl dicarbonate (3.1 mL, 13.5 mmol) was added thereto. The obtained mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - n-hexane to give
20 tert-butyl [6-benzyloxy-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (4.27 g, 89.5%) as crystals.

Melting point 138-139°C.

Elemental analysis for C₃₂H₃₅N₂O₄F

Calculated: C, 72.43; H, 6.65; N, 5.28.
35 Found: C, 72.27; H, 6.38; N, 5.22.

- ¹H-NMR(CDCl₃) δ: 0.99 (6H, d, J=7.0 Hz), 1.43 (9H, s),
2.16-2.30 (1H, m), 3.83-3.94 (1H, m), 3.99-4.38 (3H, m),
4.58 (1H, bs), 4.95 (2H, s), 6.33 (1H, d, J=2.4 Hz),
7.11 (1H, dd, J=2.4, 9.0 Hz), 7.16-7.38 (8H, m), 7.43-
⁵ 7.54 (1H, m), 8.39 (1H, d, J=9.0 Hz).
- (9) A suspension of tert-butyl [6-benzyloxy-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (3.98 g, 7.5 mmol) and 5% palladium carbon (1.5 g) in ethanol (50 mL) was stirred
¹⁰ under a hydrogen atmosphere at room temperature for 2 h. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The obtained crystals were recrystallized from tetrahydrofuran - diisopropyl ether to give tert-butyl [4-(2-fluorophenyl)-6-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (3.11 g, 94.2%) as crystals.
- Melting point 163-164°C..
- Elemental analysis for C₂₅H₂₉N₂O₄F 0.5H₂O
- ²⁰ Calculated: C, 66.80; H, 6.73; N, 6.23.
Found: C, 66.80; H, 6.93; N, 6.28.
- ¹H-NMR(CDCl₃) δ: 0.96 (6H, d, J=6.6 Hz), 1.42 (9H, s),
2.11-2.28 (1H, m), 3.82-3.92 (1H, m), 4.02-4.21 (2H, m),
4.28-4.38 (1H, m), 4.60 (1H, bs), 6.37 (1H, d, J=2.2 Hz),
²⁵ 7.08 (1H, dd, J=2.2, 8.8 Hz), 7.13-7.23 (4H, m), 7.34-
7.47 (1H, m), 8.28 (1H, d, J=8.8 Hz).
- (10) A solution of tert-butyl [4-(2-fluorophenyl)-6-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.44 g, 1 mmol), 2-
³⁰ iodoacetamide (0.37 g, 2 mmol) and 1,8-diazabicyclo[5.4.0]-7-undecene (0.30 mL, 2 mmol) in N,N-dimethylformamide (10 mL) was stirred at 80°C for 10 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine,
³⁵ dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by

silica gel column chromatography to give tert-butyl [6-(2-amino-2-oxoethoxy)-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.30 g, 61.2%) as crystals.

⁵ Melting point 186-188°C.

Elemental analysis for C₂₇H₃₂N₃O₅F 0.25H₂O

Calculated: C, 64.59; H, 6.52; N, 8.37.

Found: C, 64.74; H, 6.32; N, 7.97.

¹H-NMR(CDCl₃) δ: 0.99 (3H, d, J=7.0 Hz), 1.00 (3H, d,

¹⁰ J=6.8 Hz), 1.43 (9H, s), 2.15-2.32 (1H, m), 3.85-4.00 (4H, m), 4.35 (2H, s), 4.59 (1H, bs), 5.70 (1H, bs), 6.29 (1H, d, J=2.4 Hz), 6.50 (1H, bs), 7.07 (1H, dd, J=2.4, 9.0 Hz), 7.21-7.37 (3H, m), 7.46-7.58 (1H, m), 8.44 (1H, d, J=9.0 Hz).

¹⁵ (11) To a solution of tert-butyl [6-(2-amino-2-oxoethyl)-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.25 g, 0.5 mmol) in ethyl acetate (5 mL) was added a solution of 4N hydrogen chloride in ethyl acetate (5 mL), and the

²⁰ obtained solution was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure. The residue was poured into saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 2-[(3-(aminomethyl)-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl)oxy]acetamide (0.02 g, 10.0%) as an

²⁵ amorphous.

¹H-NMR(CDCl₃) δ: 1.00 (3H, d, J=6.6 Hz), 1.02 (3H, d, J=6.6 Hz), 1.66 (2H, bs), 2.18-2.32 (1H, m), 4.07-4.28 (3H, m), 4.35 (2H, s), 5.77 (1H, bs), 6.27 (1H, d, J=2.6 Hz), 6.51 (1H, bs), 7.05 (1H, dd, J=2.6, 8.8 Hz), 7.22-

³⁰ 7.35 (3H, m), 7.45-7.56 (1H, m), 8.44 (1H, d, J=8.8 Hz).

Example 155

3-(Aminomethyl)-4-(2-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone-6-carboxamide hydrochloride

(1) To a solution of tert-butyl [4-(2-fluorophenyl)-6-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-

5 isoquinolinyl)methylcarbamate (Example 8(9)) (2.42 g, 5.5 mmol) in N,N-dimethylformamide (30 mL) was added sodium hydride (0.33 g, 8.3 mmol) (60% in oil) at 0°C and the mixture was stirred at 0°C for 30 min. To the obtained mixture was added N-

10 phenyltrifluoromethanesulfonimide (2.97 g, 8.3 mmol) and the mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium

15 sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [4-(2-fluorophenyl)-2-isobutyl-1-oxo-6-trifluoromethanesulfonyloxy-1,2-dihydro-3-isoquinolinyl)methylcarbamate (2.91 g, 92.4%) as an

20 amorphous.

¹H-NMR(CDCl₃) δ: 1.00 (3H, d, J=6.6 Hz), 1.01 (3H, d, J=7.0 Hz), 1.46 (9H, s), 2.17-2.31 (1H, m), 3.89-3.99 (1H, m), 4.07-4.27 (2H, m), 4.33-4.44 (1H, m), 4.59 (1H, bs), 6.79 (1H, d, J=2.2 Hz), 7.21-7.44 (1H, m), 7.48-25 7.60 (1H, m), 8.57 (1H, d, J=8.8 Hz).

(2) A mixed solution of tert-butyl [4-(2-fluorophenyl)-2-isobutyl-1-oxo-6-trifluoromethanesulfonyloxy-1,2-dihydro-3-isoquinolinyl)methylcarbamate (2.86 g, 5 mmol),

30 1,1'-bis(diphenylphosphino)ferrocene (0.14 g, 0.25 mmol), triethylamine (0.77 mL, 5.5 mmol) and palladium acetate (56 mg, 0.25 mmol) in tetrahydrofuran (20 mL) and methanol (20 mL) was stirred with heating at 100°C under a carbon monoxide atmosphere at 5 atm for 1 h. The reaction mixture was poured into water and extracted

35 with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium

sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give methyl 3-[[(tert-butoxycarbonyl)amino]methyl]-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-

⁵ isoquinolinecarboxylate (2.23 g, 92.5%) as crystals. Melting point 180-181°C.

Elemental analysis for C₂₇H₃₁N₂O₅F

Calculated: C, 67.20; H, 6.48; N, 5.81.

Found: C, 66.95; H, 6.55; N, 5.75.

¹⁰ ¹H-NMR(CDCl₃) δ: 1.00 (3H, d, J=6.6 Hz), 1.01 (3H, d, J=6.6 Hz), 1.43 (9H, s), 2.19-2.33 (1H, m), 3.86 (3H, s), 3.89-4.43 (4H, m), 4.62 (1H, bs), 7.23-7.38 (3H, m), 7.47-7.58 (1H, m), 7.46 (1H, d, J=1.5 Hz), 8.06 (1H, dd, J=1.5, 8.4 Hz), 8.53 (1H, d, J=8.4 Hz).

¹⁵ (3) To a solution of methyl 3-[[(tert-butoxycarbonyl)amino]methyl]-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylate (1.93 g, 4 mmol) in tetrahydrofuran (10 mL) and methanol (10 mL) was added 1N sodium hydroxide (8 mL). The

²⁰ obtained mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under

²⁵ reduced pressure. The obtained crystals were recrystallized from ethyl acetate - isopropyl ether to give 3-[[(tert-butoxycarbonyl)amino]methyl]-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid (1.77 g, 94.7%) as crystals.

³⁰ Melting point 213-214°C.

Elemental analysis for C₂₆H₂₉N₂O₅F

Calculated: C, 66.65; H, 6.24; N, 5.98.

Found: C, 66.51; H, 6.50; N, 5.99.

¹H-NMR(CDCl₃) δ: 1.00 (3H, d, J=6.8 Hz), 1.01 (3H, d, J=6.6 Hz), 1.45 (9H, s), 2.19-2.32 (1H, m), 4.84 (1H, bs), 7.22-7.34 (3H, m), 7.46-7.57 (1H, m), 7.65 (1H, s),

8.05 (1H, d, J=8.4 Hz), 8.51 (1H, d, J=8.4 Hz).

(4) A solution of 3-[(tert-butoxycarbonyl)amino]methyl]-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid

- 5 (0.70 g, 1.5 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.58 g, 3 mmol) and 1-hydroxybenzotriazole ammonium salt (0.46 g, 3 mmol) in N,N-dimethylformamide (10 mL) was stirred at room temperature for 3 h. The reaction mixture was
10 poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from tetrahydrofuran-diisopropyl ether to give 3-
15 [(tert-butoxycarbonyl)amino]methyl]-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxamide (0.67 g, 95.7%) as crystals.

Melting point: 232-233°C.

Elemental analysis for C₂₆H₃₀N₃O₄F

20 Calculated: C, 66.79; H, 6.47; N, 8.99.

Found: C, 66.39; H, 6.75; N, 8.93.

¹H-NMR(CDCl₃) = δ: 0.99 (3H, d, J=6.6 Hz), 1.01 (3H, d, J=6.6 Hz), 1.44 (9H, s), 2.22-2.30 (1H, m), 3.92-4.19 (3H, m), 4.32-4.40 (1H, m), 4.69 (1H, bs), 5.78 (1H, bs),
25 6.10 (1H, bs), 7.23-7.35 (3H, m), 7.40 (1H, d, J=1.5 Hz), 7.47-7.54 (1H, m), 7.77 (1H, dd, J=1.5, 8.4 Hz), 8.49 (1H, d, J=8.4 Hz).

(5) To a solution of 3-[(tert-butoxycarbonyl)amino]methyl]-4-(2-fluorophenyl)-2-

- 30 isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxamide (0.37 g, 0.8 mmol) in ethyl acetate (5 mL) was added a solution of 4N hydrogen chloride in ethyl acetate (5 mL) and the obtained solution was stirred at room temperature for 1 h. The reaction mixture was
35 concentrated under reduced pressure, and the precipitated crystals were recrystallized from methanol

- diethyl ether to give 3-(aminomethyl)-4-(2-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone-6-carboxamide hydrochloride (0.30 g, 93.8%) as crystals.
Melting point 216-218°C.

⁵ Elemental analysis for C₂₁H₂₃N₃O₂ClF 2H₂O

Calculated: C, 57.34; H, 6.19; N, 9.55.

Found: C, 57.41; H, 5.93; N, 9.71.

¹H-NMR(DMSO-d₆) δ: 0.92 (3H, d, J=6.6 Hz), 0.93 (3H, d, J=6.6 Hz), 2.01-2.16 (1H, m), 3.62-3.80 (1H, m), 4.02-

¹⁰ 4.23 (3H, m), 7.43-7.66 (6H, m), 8.03 (1H, d, J=8.4 Hz), 8.21 (1H, bs), 8.38 (1H, d, J=8.4 Hz), 8.72 (3H, bs).

Example 156

3-(Aminomethyl)-4-(2-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone-6-carbonitrile hydrochloride

¹⁵ (1) A solution of 3-[[(tert-butoxycarbonyl)amino]methyl]-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxamide (Example 10 (4)) (0.23 g, 0.5 mmol) and cyanuric chloride (0.28 g, 1.5 mmol) in N,N-dimethylformamide (10 mmol) was stirred at 0°C for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate - n-hexane to give tert-butyl [6-cyano-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.19 g, 86.4%) as crystals.

Melting point 191-192°C.

³⁰ Elemental analysis for C₂₆H₂₈N₃O₃F

Calculated: C, 69.47; H, 6.28; N, 9.35..

Found: C, 69.37; H, 6.42; N, 9.24.

¹H-NMR(CDCl₃) δ: 1.00 (3H, d, J=6.6 Hz), 1.01 (3H, d, J=7.0 Hz), 1.43 (9H, s), 2.18-2.32 (1H, m), 3.89-4.05

³⁵ (1H, m), 4.07-4.44 (3H, m), 4.58 (1H, bs), 7.20-7.40 (4H, m), 7.50-7.61 (1H, m), 7.67 (1H, dd, J=1.6, 8.2 Hz),

8.56 (1H, d, J=8.2 Hz).

(2) To a solution of tert-butyl [6-cyano-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.13 g, 0.3 mmol) in

- 5 ethyl acetate (5 mL) was added a solution of 4N hydrogen chloride in ethyl acetate (5 mL) and the obtained solution was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the precipitated crystals were recrystallized from
10 methanol-diethyl ether to give 3-(aminomethyl)-4-(2-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone-6-carbonitrile hydrochloride (0.11 g, 91.7%) as crystals. Melting point 228-230°C.

¹H-NMR(DMSO-d₆) δ: 0.92 (3H, d, J=6.6 Hz), 0.94 (3H, d,

- 15 J=6.6 Hz), 1.99-2.19 (1H, m), 3.76-3.83 (1H, m), 3.96-4.22 (3H, m), 7.30 (1H, d, J=1.4 Hz), 7.41-7.72 (4H, m), 7.99 (1H, dd, J=1.4, 8.4 Hz), 8.49 (1H, d, J=8.4 Hz), 8.74 (3H, bs).

Example 157

- 20 2-[[3-(Aminomethyl)-4-(3-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]oxy]acetamide hydrochloride
(1) A mixture of methyl 6-benzyloxy-2-isobutyl-1-oxo-4-trifluoromethanesulfonyloxy-1,2-dihydro-3-isoquinolinecarboxylate (10.26 g, 20 mmol), 3-
25 fluorophenylboronic acid (3.36 g, 24 mmol) and sodium carbonate (5.30 g, 50 mmol) in toluene (50 mL), ethanol (10 mL) and water (10 mL) was stirred under an argon atmosphere at room temperature for 30 min. To the obtained mixture was added
30 tetrakis(triphenylphosphine)palladium (1.16 g, 1 mmol) and the mixture was refluxed under heating under an argon atmosphere for 12 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was
35 dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by

silica gel column chromatography to give methyl 6-benzyloxy-4-(3-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (6.31 g, 68.7%) as crystals.

5 Melting point 127-128°C.

Elemental analysis for C₂₈H₂₆NO₄F

Calculated: C, 73.19; H, 5.70; N, 3.05.

Found: C, 73.03; H, 5.63; N, 2.77.

10 ¹H-NMR(CDCl₃) δ: 0.91 (6H, d, J=7.0 Hz), 2.04-2.19 (1H, m), 3.50 (3H, s), 3.8-4.00 (2H, m), 4.99 (2H, s), 6.57 (1H, d, J=2.4 Hz), 6.96-7.21 (4H, m), 7.24-7.46 (6H, m), 8.43 (1H, d, J=8.8 Hz).

(2) To a solution of methyl 6-benzyloxy-4-(3-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-

15 isoquinolinecarboxylate (5.97 g, 13 mmol) in tetrahydrofuran (50 mL) and methanol (50 mL) was added an aqueous solution (10 mL) of lithium hydroxide monohydrate (1.64 g, 39 mmol). The obtained mixture was refluxed under heating for 12 h. The reaction mixture

20 was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (50 mL), and

25 oxalyl chloride (1.0 mL, 12 mmol) and N,N-dimethylformamide (3 drops) were added thereto. The mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in tetrahydrofuran (30 mL).

30 The obtained solution was added dropwise to a suspension of sodium tetrahydroborate (1.32 g, 35 mmol) in 1,2-dimethoxyethane (30 mL) at 0°C. The obtained mixture was stirred at 0°C for 1 h. The reaction mixture was poured into 1N hydrochloric acid and extracted with

35 ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under

reduced pressure. The residue was purified by silica gel column chromatography to give 6-benzyloxy-4-(3-fluorophenyl)-3-hydroxymethyl-2-isobutyl-1(2H)-isoquinolinone (1.39 g, 32.2%) as crystals.

5 Melting point 146-146.5°C.

Elemental analysis for C₂₇H₂₆NO₃F

Calculated: C, 75.15; H, 6.07; N, 3.25.

Found: C, 74.87; H, 6.06; N, 3.12.

¹H-NMR(CDCl₃) δ: 0.94 (6H, d, J=6.6 Hz), 2.11-2.28 (1H,

10 m), 2.58 (1H, bs), 4.16 (2H, d, J=7.6 Hz), 4.41 (2H, d, J=5.8 Hz), 4.91 (2H, s), 6.31 (1H, d, J=2.2 Hz), 6.95-7.37 (9H, m), 7.44-7.52 (1H, m), 8.25 (1H, d, J=8.8 Hz).

(3) To a suspension of 6-benzyloxy-4-(3-fluorophenyl)-3-hydroxymethyl-2-isobutyl-1(2H)-isoquinolinone (3.88 g, 9

15 mmol) in toluene (30 mL) was added thionyl chloride (1.3 mL, 18 mmol). The obtained mixture was refluxed under heating for 2 h. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed

20 with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 6-benzyloxy-3-chloromethyl-4-(3-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone (3.71 g, 91.8%) as an oil.

¹H-NMR(CDCl₃) δ: 0.99 (6H, d, J=6.6 Hz), 2.13-2.31 (1H,

25 m), 4.14 (2H, d, J=7.2 Hz), 4.35 (2H, s), 4.96 (2H, s), 6.37 (1H, d, J=2.2 Hz), 6.98-7.32 (9H, m), 7.42-7.53 (1H, m), 8.40 (1H, d, J=8.8 Hz).

(4) A solution of 6-benzyloxy-3-chloromethyl-4-(3-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone (3.60 g, 8

30 mmol) and potassium phthalimide (2.22 g, 12 mmol) in N,N-dimethylformamide (30 mL) was stirred at room temperature for 6 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried

35 over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were

recrystallized from ethyl acetate - diisopropyl ether to give 2-[(6-benzyloxy-4-(3-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl]-1H-isoindole-1,3(2H)-dione (3.95 g, 88.2%) as crystals.

5 $^1\text{H-NMR}(\text{CDCl}_3)$ δ : 0.98 (6H, d, $J=6.6$ Hz), 2.10-2.27 (1H, m), 4.03 (2H, d, $J=4.4$ Hz), 4.75 (2H, s), 4.92 (2H, s), 6.32 (1H, d, $J=2.6$ Hz), 6.98-7.14 (4H, m), 7.21-7.40 (6H, m), 7.68-7.78 (4H, m), 8.38 (1H, d, $J=8.8$ Hz).

(5) To a solution of 2-[(6-benzyloxy-4-(3-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl]-1H-isoindole-1,3(2H)-dione (3.92 g, 7 mmol) in ethanol (50 mL) was added hydrazine monohydrate (1.0 mL, 21 mmol).

10 The obtained mixture was refluxed under heating for 2 h.

The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (30 mL) and di-t-butyl dicarbonate (2.4

20 mL, 10.5 mmol) was added. The obtained mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under

25 reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [(6-benzyloxy-4-(3-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (3.47 g, 93.5%) as crystals.

30 Melting point 180-181°C.

Elemental analysis for $C_{32}H_{35}N_2O_4F$

Calculated: C, 72.43; H, 6.65; N, 5.28.

Found: C, 72.30; H, 6.48; N, 5.32.

35 $^1\text{H-NMR}(\text{CDCl}_3)$ δ : 0.98 (6H, d, $J=6.6$ Hz), 1.43 (9H, s), 2.15-2.28 (1H, m), 4.02 (2H, d, $J=7.4$ Hz), 4.16 (2H, d, $J=5.0$ Hz), 4.94 (2H, s), 6.31 (1H, d, $J=2.6$ Hz), 6.89-

7.35 (9H, m), 7.41-7.52 (1H, m), 8.36 (1H, d, J=8.8 Hz).

(6) A suspension of tert-butyl [6-benzyloxy-4-(3-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (3.18 g, 6 mmol) and 5%

⁵ palladium carbon (1.0 g) in tetrahydrofuran (20 mL) and ethanol (20 mL) was stirred under a hydrogen atmosphere at room temperature for 2 h. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The obtained crystals were recrystallized

¹⁰ from ethyl acetate - n-hexane to give tert-butyl [4-(3-fluorophenyl)-6-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (2.54 g, 96.2%) as crystals.

Melting point 161-163°C.

¹⁵ Elemental analysis for C₂₅H₂₉N₂O₄F

Calculated: C, 68.16; H, 6.64; N, 6.36.

Found: C, 67.91; H, 6.89; N, 6.38.

¹H-NMR(CDCl₃) δ: 0.96 (6H, d, J=6.6 Hz), 1.42 (9H, s), 2.14-2.24 (1H, m), 4.01 (2H, d, J=5.7 Hz), 4.18 (2H, d, J=4.5 Hz), 4.52 (1H, bs), 6.34 (1H, d, J=2.1 Hz), 6.94-7.13 (4H, m), 7.38-7.46 (1H, m), 7.87 (1H, bs), 8.26 (1H, d, J=8.4 Hz).

(7) A solution of tert-butyl [(4-(3-fluorophenyl)-6-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-

²⁵ isoquinolinyl)methylcarbamate (0.44 g, 1 mmol), 2-iodoacetamide (0.37 g, 2 mmol) and 1,8-diazabicyclo[5.4.0]-7-undecene (0.3 mL, 2 mmol) in N,N-dimethylacetamide (10 mL) was stirred at 70°C for 10 h. The reaction mixture was poured into water and extracted

³⁰ with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by

silica gel column chromatography to give tert-butyl [6-(2-amino-2-oxoethoxy)-4-(3-fluorophenyl)-2-isobutyl-1-

³⁵ oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.21 g, 42.9%) as crystals.

Melting point 241-242°C.

Elemental analysis for C₂₇H₃₂N₃O₅F 0.25H₂O

Calculated: C, 64.59; H, 6.52; N, 8.37.

Found: C, 64.61; H, 6.66; N, 8.07.

⁵ ¹H-NMR(CDCl₃) δ: 0.99 (6H, d, J=6.6 Hz), 1.43 (9H, s), 2.19-2.34 (1H, m), 4.04 (2H, d, J=7.0 Hz), 4.35 (2H, s), 4.86 (1H, bs), 6.15 (1H, bs), 6.31 (1H, d, J=2.6 Hz), 6.59 (1H, bs), 6.99-7.25 (4H, m), 7.45-7.54 (1H, m), 8.42 (1H, d, J=9.2 Hz).

¹⁰ (8) To a solution of tert-butyl [6-(2-amino-2-oxoethoxy)-4-(3-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.15 g, 0.3 mmol) in ethyl acetate (5 mL) was added a solution of 4N hydrogen chloride in ethyl acetate (5 mL), and the obtained solution was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and crystallized from ethyl acetate - diisopropyl ether to give 2-[[3-(aminomethyl)-4-(3-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]oxy]acetamide hydrochloride (0.12 g, 92.3%) as crystals.

Melting point 209-210°C.

¹H-NMR(DMSO-d₆) δ: 0.91 (6H, d, J=6.6 Hz), 1.99-2.18 (1H, m), 3.84 (2H, bs), 3.94-4.08 (2H, m), 4.39 (2H, s), 6.29 (1H, d, J=2.2 Hz), 7.18-7.41 (5H, m), 8.27 (1H, d, J=9.2 Hz), 8.59 (3H, bs).

Example 158

3-(Aminomethyl)-4-(3-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone-6-carboxamide hydrochloride

³⁰ (1) To a solution of tert-butyl [4-(3-fluorophenyl)-6-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (Example 11 (6)) (1.76 g, 4 mmol) in N,N-dimethylformamide (20 mL) was added sodium hydride (0.19 g, 4.8 mmol)(60% in oil) at 0°C and the mixture was stirred at 0°C for 30 min. To the obtained mixture was added N-

phenyltrifluoromethanesulfonimide (1.71 g, 4.8 mmol) and the mixture was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with 5 water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [4-(3-fluorophenyl)-2-isobutyl-1-oxo-6-trifluoromethanesulfonyloxy-1,2-dihydro-3-isoquinolinyl]methylcarbamate (2.30 g, 100%) as an oil. ¹H-NMR(CDCl₃) δ: 0.99 (6H, d, J=6.6 Hz), 1.43 (9H, s), 2.14-2.28 (1H, m), 4.08 (2H, d, J=9.0 Hz), 4.23 (2H, d, J=5.6 Hz), 4.50 (1H, bs), 6.80 (1H, d, J=2.6 Hz), 6.96-7.08 (2H, m), 7.18-7.59 (3H, m), 8.55 (1H, d, J=8.8 Hz). 10 15 (2) A mixed solution of tert-butyl [4-(3-fluorophenyl)-2-isobutyl-1-oxo-6-trifluoromethanesulfonyloxy-1,2-dihydro-3-isoquinolinyl]methylcarbamate (2.29 g, 4 mmol), 1,1'-bis(diphenylphosphino)ferrocene (0.11 g, 0.2 mmol), triethylamine (0.6 mL, 4.4 mmol) and palladium acetate 20 (45 mg, 0.2 mmol) in tetrahydrofuran (20 mL) and methanol (20 mL) was stirred with heating at 100°C under a carbon monoxide atmosphere at 5 atm for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with 25 water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give methyl 3-[(tert-butoxycarbonyl)amino]methyl]-4-(3-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylate (1.76 g, 91.2%) as crystals. Melting point 206-208°C. 30 Elemental analysis for C₂₇H₃₁N₂O₅F
Calculated: C, 67.20; H, 6.48; N, 5.81.
Found: C, 66.96; H, 6.63; N, 5.59. 35 ¹H-NMR(CDCl₃) δ: 1.00 (6H, d, J=6.6 Hz), 1.44 (9H, s), 2.18-2.30 (1H, m), 3.87 (3H, s), 4.08 (2H, d, J=7.2 Hz),

4.21 (2H, d, J=5.1 Hz), 4.54 (1H, bs), 6.99-7.08 (2H, m),
7.18-7.27 (1H, m), 7.62 (1H, d, J=1.2 Hz), 8.04 (1H, dd,
J=1.2, 8.4 Hz), 8.50 (1H, d, J=8.4 Hz).

- (3) To a solution of methyl 3-[(tert-
5 butoxycarbonyl)amino]methyl]-4-(3-fluorophenyl)-2-
isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylate
(1.45 g, 3 mmol) in tetrahydrofuran (10 mL) and methanol
(10 mL) was added 1N sodium hydroxide (6 mL). The
obtained mixture was stirred at room temperature for 2 h.
10 The reaction mixture was poured into water, acidified
with 1N hydrochloric acid and extracted with ethyl
acetate. The extract was washed with brine, dried over
anhydrous magnesium sulfate and concentrated under
reduced pressure. The residue was crystallized from
15 ethyl acetate - n-hexane to give 3-[(tert-
butoxycarbonyl)amino]methyl]-4-(3-fluorophenyl)-2-
isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid
(1.34 g, 95.7%) as crystals.
Melting point 206-207°C.
20 Elemental analysis for C₂₆H₂₉N₂O₅F
Calculated: C, 66.65; H, 6.24; N, 5.98.
Found: C, 66.39; H, 6.33; N, 5.63.
¹H-NMR(CDCl₃) δ: 0.99 (6H, d, J=6.6 Hz), 1.48 (9H, s),
2.10-2.29 (1H, m), 4.05 (2H, d, J=7.4 Hz), 4.17 (2H, d,
25 J=4.4 Hz), 5.49 (1H, bs), 7.05-7.27 (3H, m), 7.44-7.58
(2H, m), 7.86-7.90 (1H, m), 8.36 (1H, d, J=8.4 Hz).
(4) A solution of 3-[(tert-
butoxycarbonyl)amino]methyl]-4-(3-fluorophenyl)-2-
isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid
30 (1.17 g, 2.5 mmol), 1-ethyl-3-(3-
dimethylaminopropyl)carbodiimide hydrochloride (0.96 g,
5 mmol) and 1-hydroxybenzotriazole ammonium salt (0.76 g,
5 mmol) in N,N-dimethylformamide (10 mL) was stirred at
room temperature for 2 h. The reaction mixture was
35 poured into water and extracted with ethyl acetate. The
extract was washed with brine, dried over anhydrous

magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from tetrahydrofuran - diisopropyl ether to give 3-[[*(tert*-butoxycarbonyl)amino]methyl]-4-(3-fluorophenyl)-

- ⁵ 2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxamide (0.81 g, 69.8%) as crystals.

Melting point 147-149°C.

Elemental analysis for C₂₆H₃₀N₃O₄F 0.5H₂O

Calculated: C, 65.53; H, 6.56; N, 8.82.

- ¹⁰ Found: C, 65.91; H, 6.44; N, 8.87.

¹H-NMR(CDCl₃) δ: 1.00 (6H, d, J=7.0 Hz), 1.44 (9H, s), 2.14-2.30 (1H, m), 4.07 (2H, d, J=7.4 Hz), 4.19 (2H, d, J=5.6 Hz), 4.73 (1H, bs), 5.77 (1H, bs), 6.11 (1H, bs), 6.98-7.25 (3H, m), 7.37 (1H, d, J=1.8 Hz), 7.45-7.56 (1H, m), 7.72 (1H, dd, J=1.8, 8.4 Hz), 8.42 (1H, d, J=8.4 Hz).

(5) To a solution of 3-[[*(tert*-butoxycarbonyl)amino]methyl]-4-(3-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxamide (0.28 g, 0.6 mmol) in ethyl acetate (5 mL) was added a

- ²⁰ solution of 4N hydrogen chloride in ethyl acetate (5 mL) and the obtained solution was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the precipitated crystals were recrystallized from methanol

- ²⁵ - diethyl ether to give 3-(aminomethyl)-4-(3-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone-6-carboxamide hydrochloride (0.22 g, 91.7%) as crystals.

Melting point 292-293°C.

Elemental analysis for C₂₁H₂₃N₃O₂ClF 0.5H₂O

- ³⁰ Calculated: C, 61.09; H, 5.86; N, 10.18.

Found: C, 60.79; H, 6.09; N, 10.04.

¹H-NMR(DMSO-d₆) δ: 0.93 (6H, d, J=6.6 Hz), 2.02-2.19 (1H, m), 3.87 (2H, bs), 4.00-4.20 (2H, m), 7.26-7.45 (4H, m), 7.58-7.69 (2H, m), 8.01 (1H, dd, J=1.6, 8.4 Hz), 8.19

- ³⁵ (1H, bs), 8.38 (1H, d, J=8.4 Hz), 8.61 (3H, bs).

Example 159

(E)-3-[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-2-propenamide hydrochloride

(1) To a solution of 3-[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-4-phenyl-

5 1,2-dihydro-6-isoquinolinecarboxylic acid (6.31 g, 14 mmol) and N-methylmorpholine (1.8 mL, 16.8 mmol) in tetrahydrofuran (50 mL) was added ethyl chloroformate (1.6 mL, 16.8 mmol) at 0°C and the mixture was stirred at 0°C for 10 min. To the obtained mixture were added
10 sodium tetrahydroborate (1.59 g, 42 mmol) and methanol (5 mL) and the mixture was stirred at 0°C for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated
15 under reduced pressure. The precipitated crystals were recrystallized from ethyl acetate - diisopropyl ether to give tert-butyl (6-hydroxymethyl-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (4.73 g, 77.4%) as crystals.

20 Melting point 169-170°C.

Elemental analysis for C₂₆H₃₂N₂O₄

Calculated: C, 71.53; H, 7.39; N, 6.42.

Found: C, 71.25; H, 7.49; N, 6.35.

25 ¹H-NMR(CDCl₃) δ: 0.99 (6H, d, J=6.6 Hz), 1.43 (9H, s), 2.04 (1H, bs), 2.16-2.29 (1H, m), 4.06 (2H, d, J=7.4 Hz), 4.18 (2H, d, J=5.4 Hz), 4.64 (2H, d, J=6.0 Hz), 4.66 (1H, bs), 6.89 (1H, s), 7.22-7.27 (2H, m), 7.49-7.54 (4H, m), 8.38 (1H, d, J=8.0 Hz).

20 (2) To a solution of tert-butyl (6-hydroxymethyl-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (4.58 g, 10.5 mmol) in tetrahydrofuran (50 mL) was added manganese dioxide (13.7 g) and the mixture was stirred at room temperature for 12 h. Manganese dioxide was filtered off and the
35 filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography

to give tert-butyl (6-formyl-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (4.12 g, 90.4%) as crystals.

Melting point 183-184°C.

⁵ Elemental analysis for C₂₆H₃₀N₂O₄

Calculated: C, 71.87; H, 6.96; N, 6.45.

Found: C, 71.79; H, 6.84; N, 6.36.

¹H-NMR(CDCl₃) δ: 1.02 (6H, d, J=6.6 Hz), 1.43 (9H, s), 2.19-2.32 (1H, m), 4.10 (2H, d, J=7.4 Hz), 4.24 (2H, d, ¹⁰J=5.6 Hz), 4.51 (1H, bs), 7.26-7.30 (2H, m), 7.44 (1H, d, J=1.4 Hz), 7.51-7.59 (3H, m), 7.92 (1H, dd, J=1.4, 8.2 Hz), 8.59 (1H, d, J=8.2 Hz), 9.95 (1H, s).

(3) To a solution of ethyl diethylphosphonoacetate (1.0 mL, 5 mmol) in N,N-dimethylformamide (20 mL) was added

¹⁵ sodium hydride (0.20 g, 5 mmol) (60% in oil), and the mixture was stirred at room temperature for 10 min. To the obtained mixture was added a solution of tert-butyl (6-formyl-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (2.17 g, 5 mmol) in N,N-dimethylformamide (20 mL) and the mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give ethyl (E)-3-[3-[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-2-propenate (2.03 g, 71.7%) as an amorphous.

³⁰ Melting point 147-148°C.

Elemental analysis for C₃₀H₃₆N₂O₅

Calculated: C, 71.40; H, 7.19; N, 5.55.

Found: C, 71.37; H, 7.15; N, 5.43.

¹H-NMR(CDCl₃) δ: 1.01 (6H, d, J=7.0 Hz), 1.31 (3H, t, ³⁵J=7.3 Hz), 1.43 (9H, s), 2.18-2.31 (1H, m), 4.08 (2H, d, J=7.4 Hz), 4.13-4.28 (4H, m), 4.53 (1H, bs), 6.37 (1H, d,

J=16.2 Hz), 7.00 (1H, d, J=1.4 Hz), 7.18-7.28 (2H, m), 7.44-7.67 (5H, m), 8.44 (1H, d, J=8.0 Hz).

(4) To a solution of ethyl (E)-3-[3-[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-4-phenyl-
5 1,2-dihydro-6-isoquinolinyl]-2-propenate (0.70 g, 1.4 mmol) in tetrahydrofuran (10 mL) and ethanol (10 mL) was added 1N sodium hydroxide (3 mL). The obtained mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water, acidified with 1N
10 hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - n-hexane to give (E)-3-[3-[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-4-phenyl-
15 1,2-dihydro-6-isoquinolinyl]-2-propenic acid (0.56 g, 84.8%) as crystals.

Melting point 172-173°C.

Elemental analysis for C₂₈H₃₂N₂O₅

20 Calculated: C, 70.27; H, 7.16; N, 5.85.

Found: C, 70.08; H, 6.80; N, 5.65.

¹H-NMR(CDCl₃) δ: 0.99 (6H, d, J=6.6 Hz), 1.48 (9H, s), 2.16-2.24 (1H, m), 4.06 (2H, d, J=7.2 Hz), 4.15 (2H, d, J=4.0 Hz), 5.62 (1H, bs), 6.27 (1H, d, J=16.0 Hz), 6.82 (1H, s), 7.33-7.40 (3H, m), 7.48-7.58 (3H, m), 8.28 (1H, d, J=8.8 Hz).

(5) A solution of (E)-3-[3-[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-2-propenic acid (0.33 g, 0.7 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.27 g, 1.4 mmol) and 1-hydroxybenzotriazole ammonium salt (0.21 g, 1.4 mmol) in N,N-dimethylformamide (10 mL) was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous

magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give (E)-3-[3-[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-4-

5 phenyl-1,2-dihydro-6-isoquinolinyl]-2-propenamide (0.31 g, 93.9%) as crystals.

Melting point 146-147°C.

Elemental analysis for $C_{28}H_{33}N_3O_4$ 0.25H₂O

Calculated: C, 70.05; H, 7.03; N, 8.75.

10 Found: C, 70.08; H, 7.09; N, 8.64.

¹H-NMR(CDCl₃) δ: 1.00 (6H, d, J=6.6 Hz), 1.44 (9H, s), 2.16-2.24 (1H, m), 4.07 (2H, d, J=7.4 Hz), 4.19 (2H, d, J=5.6 Hz), 4.96 (1H, bs), 5.75 (1H, bs), 6.38 (1H, d, J=15.6 Hz), 6.94 (1H, s), 7.26-7.30 (2H, m), 7.40-7.56

15 (5H, m), 8.29 (1H, d, J=8.4 Hz).

(6) A solution of (E)-3-[3-[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-2-propenamide (0.24 g, 0.5 mmol) in ethyl acetate (5 mL) was added a solution of 4N

20 hydrogen chloride in ethyl acetate (5 mL), and the obtained solution was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the precipitated crystals were recrystallized from methanol - diisopropyl ether to give

25 (E)-3-[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-2-propenamide hydrochloride (0.20 g, 95.2%) as crystals.

Melting point 223-225°C.

Elemental analysis for $C_{23}H_{26}N_3O_2Cl$ 1.5H₂O

30 Calculated: C, 62.93; H, 6.66; N, 9.57.

Found: C, 63.15; H, 6.66; N, 9.34.

¹H-NMR(DMSO-d₆) δ: 0.92 (6H, d, J=6.9 Hz), 2.06-2.16 (1H, m), 3.87 (2H, d, J=4.8 Hz), 4.08 (2H, s), 6.56 (1H, d, J=16.0 Hz), 7.19 (1H, bs), 7.31 (1H, d, J=16.0 Hz),

35 7.42-7.44 (2H, m), 7.54-7.63 (3H, m), 7.69 (1H, bs), 7.78 (1H, dd, J=1.2, 8.8 Hz), 8.35 (1H, d, J=8.8 Hz),

8.62 (3H, bs).

Example 160

(E)-3-[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-2-propenamide

(1) (E)-3-[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-2-propenamide hydrochloride (Example 159 (6)) (0.13 g, 0.3 mmol) was dissolved in water (10 mL) and saturated aqueous potassium carbonate solution (10 mL) was added. The mixture was extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The precipitated crystals were recrystallized from ethyl acetate - diisopropyl ether to give (E)-3-[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-2-propenamide (0.06 g, 54.5%) as crystals.

Melting point 228-230°C.

¹H-NMR(CDCl₃) δ: 1.00 (6H, d, J=7.0 Hz), 1.47 (2H, bs), 2.19-2.33 (1H, m), 3.69 (2H, s), 4.22 (2H, d, J=7.0 Hz), 5.70 (2H, bs), 6.43 (1H, d, J=15.8 Hz), 6.99 (1H, d, J=1.5 Hz), 7.25-7.29 (2H, m), 7.47-7.55 (4H, m), 7.58 (1H, dd, J=1.5, 8.4 Hz), 8.44 (1H, d, J=8.4 Hz).

Recrystallization from ethanol - ethyl acetate gave crystals in a different crystal form.

(2) Melting point 275-276°C

Powder X-ray crystal diffraction data

Diffraction angle: 2θ(°) spacing: d value
(angstrom)

	8.66	10.2
30	13.6	6.50
	17.5	5.07
	21.4	4.15

Example 161

2-[[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]oxy]acetamide hydrochloride
(1) To a suspension of 4-benzyloxyphthalic anhydride

(2.54 g, 10 mmol) in ethanol (30 mL) was added 20% sodium ethoxide ethanol solution (3.74 g, 11 mmol) and the mixture was stirred at room temperature for 1 h. The reaction mixture was poured into 1N hydrochloric acid (150 mL) and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in N,N-dimethylformamide (200 mL) and tert-butyl 2-isobutylaminoacetate (2.25 g, 12 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (2.30 g, 12 mmol) and 1-hydroxybenzotriazole (1.84 g, 12 mmol) were added and the mixture was stirred at room temperature for 3 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in ethanol (30 mL) and a solution (6.80 g, 20 mmol) of 20% sodium ethoxide in ethanol was added thereto. The mixture was stirred at room temperature for 1 h. The reaction mixture was poured into 1N hydrochloric acid (20 mL) and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography and the component eluted earlier was concentrated to give tert-butyl 7-benzyloxy-4-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (0.40 g, 9.5%) as an oil.

³⁰ ¹H-NMR(CDCl₃) δ: 0.82 (6H, d, J=6.6 Hz), 1.78-1.87 (1H, m), 3.99 (3H, s), 4.39 (2H, d, J=7.5 Hz), 5.25 (2H, s), 7.25-7.48 (6H, m), 7.96-7.98 (1H, m), 8.10 (1H, d, J=8.7 Hz), 11.34 (1H, s).

The component eluted later was concentrated to give ³⁵ tert-butyl 6-benzyloxy-4-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (1.51 g, 35.7%) as

crystals.

Melting point 133-134°C.

Elemental analysis for C₂₅H₂₉NO₅

Calculated: C, 70.90; H, 6.90; N, 3.31.

5 Found: C, 70.84; H, 6.85; N, 3.11.

¹H-NMR(CDCl₃) δ: 0.81 (6H, d, J=6.6 Hz), 1.64 (9H, s), 1.73-1.84 (1H, m), 4.38 (2H, d, J=7.4 Hz), 5.21 (2H, s), 7.29 (1H, dd, J=2.4, 8.8 Hz), 7.35-7.51 (5H, m), 7.58 (1H, d, J=2.4 Hz), 8.37 (1H, d, J=8.8 Hz), 11.17 (1H, s).

10 (2) To a solution of tert-butyl 6-benzyloxy-4-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (6.35 g, 15 mmol) in N,N-dimethylformamide (50 mL) was added sodium hydride (0.72 g, 18 mmol) (60% in oil) at 0°C and the mixture was stirred at 0°C for 30 min. To

15 the obtained mixture was added N-phenyltrifluoromethanesulfonimide (6.43 g, 18 mmol) and the mixture was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with

20 water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl 6-benzyloxy-2-isobutyl-1-oxo-4-trifluoromethanesulfonyloxy-1,2-dihydro-3-

25 isoquinolinecarboxylate (6.62 g, 81.2%) as an oil.

¹H-NMR(CDCl₃) δ: 0.89 (6H, d, J=6.6 Hz), 1.64 (9H, s), 2.04-2.15 (1H, m), 4.03 (2H, d, J=7.4 Hz), 5.18 (2H, s), 7.20-7.56 (7H, m), 8.34 (1H, d, J=9.2 Hz).

30 (3) A mixed solution of tert-butyl 6-benzyloxy-2-isobutyl-1-oxo-4-trifluoromethanesulfonyloxy-1,2-dihydro-3-isoquinolinecarboxylate (6.52 g, 12 mmol), phenylboronic acid (1.76 g, 14.4 mmol) and sodium carbonate (3.18 g, 30 mmol) in toluene (50 mL), ethanol (10 mL) and water (10 mL) was stirred under an argon atmosphere at room temperature for 10 min. To the obtained mixture was added tetrakis(triphenylphosphine)-

palladium (0.69 g, 0.6 mmol) and the mixture was refluxed under heating under an argon atmosphere for 10 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl 6-benzyloxy-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-

10 isoquinolinecarboxylate (5.01 g, 86.4%) as crystals. Melting point 138-139°C.

Elemental analysis for $C_{31}H_{33}NO_4$

Calculated: C, 76.99; H, 6.88; N, 2.90..

Found: C, 77.04; H, 6.80; N, 2.70.

15 1H -NMR($CDCl_3$) δ : 0.94 (6H, d, $J=6.9$ Hz), 1.15 (9H, s), 2.17-2.27 (1H, m), 3.98 (2H, d, $J=7.5$ Hz), 4.95 (2H, s), 6.53 (1H, d, $J=2.4$ Hz), 7.13 (1H, dd, $J=2.4$, 8.8 Hz), 7.25-7.36 (6H, m), 7.40-7.45 (4H, m), 8.41 (1H, d, $J=8.8$ Hz).

20 (4) A solution of tert-butyl 6-benzyloxy-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinecarboxylate (9.03 g, 25 mmol) in trifluoroacetic acid (30 mL) was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure and the obtained

25 crystals were recrystallized from ethyl acetate - diisopropyl ether to give 6-benzyloxy-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinecarboxylic acid (3.50 g, 82.0%) as crystals.

30 1H -NMR($CDCl_3$) δ : 0.85 (6H, d, $J=6.6$ Hz), 2.09-2.14 (1H, m), 3.83 (2H, d, $J=7.5$ Hz), 4.96 (2H, s), 6.58 (1H, d, $J=2.4$ Hz), 7.09-7.44 (11H, m), 8.29 (1H, d, $J=8.7$ Hz).

(5) To a solution of 6-benzyloxy-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinecarboxylic acid (3.42 g, 8 mmol) in tetrahydrofuran (30 mL) were added oxalyl

35 chloride (0.84 mL, 9.6 mmol) and N,N-dimethylformamide (3 drops), and the mixture was stirred at room

temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in tetrahydrofuran (20 mL). The obtained solution was added dropwise to a suspension of sodium 5 tetrahydronate (1.06 g, 28 mmol) in 1,2-dimethoxyethane (20 mL) at 0°C. The obtained mixture was stirred at 0°C for 1 h. The reaction mixture was poured into 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over 10 anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from tetrahydrofuran - diisopropyl ether to give 6-benzyloxy-3-hydroxymethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (2.92 g, 88.5%) as crystals.

15 $^1\text{H-NMR}(\text{CDCl}_3)$ δ: 0.96 (6H, d, J=6.6 Hz), 2.16-2.40 (2H, m), 4.18 (2H, d, J=7.5 Hz), 4.43 (2H, s), 4.89 (2H, s), 6.37 (1H, d, J=2.4 Hz), 7.00 (1H, dd, J=2.4, 9.0 Hz), 7.21-7.34 (7H, m), 7.44-7.52 (3H, m), 8.30 (1H, d, J=9.0 Hz).

20 (6) To a suspension of 6-benzyloxy-3-hydroxymethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (2.89 g, 7 mmol) in toluene (30 mL) was added thionyl chloride (1.0 mL, 14 mmol). The obtained mixture was refluxed under heating for 2 h. The reaction mixture was poured into 25 saturated aqueous sodium hydrogen carbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 6-benzyloxy-3-chloromethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (2.61 g, 86.4%) as crystals.

30 $^1\text{H-NMR}(\text{CDCl}_3)$ δ: 1.00 (6H, d, J=7.0 Hz), 2.12-2.31 (1H, m), 4.16 (2H, d, J=7.4 Hz), 4.37 (2H, s), 4.93 (2H, s), 6.41 (1H, d, J=2.3 Hz), 7.13 (1H, dd, J=2.3, 9.0 Hz), 7.19-7.35 (7H, m), 7.45-7.54 (3H, m), 8.41 (1H, d, J=9.0 Hz).

35 (7) A solution of 6-benzyloxy-3-chloromethyl-2-isobutyl-

4-phenyl-1(2H)-isoquinolinone (2.59 g, 6 mmol) and potassium phthalimide (1.67 g, 9 mmol) in N,N-dimethylformamide (30 mL) was stirred at room temperature for 6 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give 2-[(6-benzyloxy-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methyl]-1H-isoindole-1,3(2H)-dione (3.04 g, 93.5%) as crystals.

Melting point 113-114°C.

Elemental analysis for C₃₅H₃₀N₂O₄ 0.25H₂O

Calculated: C, 76.83; H, 5.62; N, 5.12.
Found: C, 76.68; H, 5.79; N, 4.93.
¹H-NMR(CDCl₃) δ: 0.99 (6H, d, J=6.4 Hz), 2.14-2.28 (1H, m), 4.04 (2H, d, J=8.4 Hz), 4.76 (2H, s), 4.91 (2H, s), 6.36 (1H, d, J=2.6 Hz), 7.10 (1H, dd, J=2.6, 8.8 Hz), 7.20-7.39 (10H, m), 7.66-7.76 (4H, m), 8.39 (1H, d, J=8.8 Hz).

(8) To a solution of 2-[(6-benzyloxy-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methyl]-1H-isoindole-1,3(2H)-dione (2.98 g, 5.5 mmol) in ethanol (30 mL) was added hydrazine monohydrate (0.8 mL, 16.5 mmol). The obtained mixture was refluxed under heating for 1 h. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 mL) and di-t-butyl dicarbonate (1.9 mL, 8.3 mmol) was added thereto. The obtained mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over

anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give tert-butyl (6-benzyloxy-2-isobutyl-1-oxo-4-phenyl-
5 1,2-dihydro-3-isoquinolinyl)methylcarbamate (2.29 g, 81.2%) as crystals.

Melting point 141-142°C.

Elemental analysis for $C_{32}H_{35}N_2O_4$

Calculated: C, 74.97; H, 7.08; N, 5.46.

10 Found: C, 74.60; H, 7.13; N, 5.45.

1H -NMR(CDCl₃) δ: 0.99 (6H, d, J=7.0 Hz), 1.42 (9H, s), 2.16-2.30 (1H, m), 4.03 (2H, d, J=7.4 Hz), 4.17 (2H, d, J=5.6 Hz), 4.45 (1H, bs), 4.92 (2H, s), 6.35 (1H, d, J=2.4 Hz), 7.09 (1H, dd, J=2.4, 9.0 Hz), 7.17-7.37 (7H, m), 7.47-7.52 (3H, m), 8.38 (1H, d, J=9.0 Hz).

(9) A suspension of tert-butyl (6-benzyloxy-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (2.05 g, 4 mmol) and 5% palladium carbon (0.6 g) in tetrahydrofuran (10 mL)
20 and ethanol (10 mL) was stirred under a hydrogen atmosphere at room temperature for 2 h. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give tert-butyl (6-hydroxy-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (1.56 g, 92.3%) as crystals.

Melting point 218-219°C.

Elemental analysis for $C_{25}H_{30}N_2O_4$

30 Calculated: C, 71.07; H, 7.16; N, 6.63.

Found: C, 70.85; H, 7.10; N, 6.62.

1H -NMR(CDCl₃) δ: 0.97 (6H, d, J=6.8 Hz), 1.42 (9H, s), 2.14-2.24 (1H, m), 4.02 (2H, d, J=7.2 Hz), 4.18 (2H, d, J=5.4 Hz), 4.47 (1H, bs), 6.33 (1H, d, J=2.4 Hz), 7.03 (1H, dd, J=2.4, 8.8 Hz), 7.20-7.27 (2H, m), 7.43-7.46 (3H, m), 7.97 (1H, bs), 8.30 (1H, d, J=8.8 Hz).

- (10) A solution of tert-butyl (6-hydroxy-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.63 g, 1.5 mmol), 2-iodoacetamide (0.43 g, 2.3 mmol) and 1,8-diazabicyclo[5.4.0]-7-undecene (0.34 mL, 2.3 mmol) in N,N-dimethylformamide (10 mL) was stirred at 80°C for 10 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl 6-(2-amino-2-oxoethoxy)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.32 g, 44.4%) as crystals.
Melting point 226-227°C.
- Elemental analysis for C₂₇H₃₃N₃O₅
Calculated: C, 67.62; H, 6.94; N, 8.76.
Found: C, 67.36; H, 6.73; N, 8.60.
¹H-NMR(DMSO-d₆) δ: 0.89 (6H, d, J=6.6 Hz), 1.38 (9H, s), 2.07-2.21 (1H, m), 3.88 (2H, d, J=6.6 Hz), 3.95 (2H, d, J=4.0 Hz), 4.34 (2H, s), 6.30 (1H, d, J=2.4 Hz), 7.13 (1H, dd, J=2.4, 8.8 Hz), 7.34-7.52 (8H, m), 8.24 (1H, d, J=8.8 Hz).
- (11) To a solution of tert-butyl [6-(2-amino-2-oxoethoxy)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.24 g, 0.5 mmol) in ethyl acetate (5 mL) was added a solution of 4N hydrogen chloride in ethyl acetate (5 mL) and the obtained solution was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the precipitated crystals were recrystallized from methanol-diethyl ether to give 2-[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]oxy]acetamide hydrochloride (0.19 g, 95.0%) as crystals.
Melting point 185-186°C.
Elemental analysis for C₂₂H₂₆N₃O₃Cl 0.5H₂O

Calculated: C, 62.23; H, 6.44; N, 9.75.

Found: C, 62.18; H, 6.40; N, 9.89.

¹H-NMR(DMSO-d₆) δ: 0.91 (6H, d, J=6.6 Hz), 2.01-2.18 (1H, m), 3.37 (2H, bs), 3.85 (2H, bs), 4.05 (2H, d, J=6.8 Hz),
⁵ 4.36 (2H, s), 6.30 (1H, d, J=2.0 Hz), 7.19 (1H, dd, J=2.0, 8.8 Hz), 7.36-7.40 (2H, m), 7.52-7.58 (3H, m), 8.28 (1H, d, J=8.8 Hz), 8.55 (3H, s).

Example 162

2-[[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]oxy]acetamide
¹⁰ (1) To a solution of tert-butyl [6-(2-amino-2-oxoethoxy)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.38 g, 0.8 mmol) in ethyl acetate (5 mL) was added a solution of 4N hydrogen chloride in ethyl acetate (5 mL) and the obtained solution was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the residue was suspended in 1N aqueous sodium hydroxide solution. The suspension was stirred at room temperature for 10 min, and the reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The precipitated crystals were recrystallized from ethyl acetate - diisopropyl ether to give 2-[[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]oxy]acetamide (0.19 g, 63.3%) as crystals. Melting point 161-163°C.

Elemental analysis for C₂₂H₂₅N₃O₃ 0.25H₂O

³⁰ Calculated: C, 68.82; H, 6.69; N, 10.94.

Found: C, 69.02; H, 6.71; N, 10.80.

¹H-NMR(CDCl₃) δ: 0.99 (6H, d, J=7.0 Hz), 1.29 (2H, bs), 2.18-3.66 (2H, s), 4.19 (2H, d, J=7.4 Hz), 4.32 (2H, s), 5.81 (1H, bs), 6.30 (1H, d, J=2.4 Hz), 6.51 (1H, bs),
³⁵ 7.03 (1H, dd, J=2.4, 8.8 Hz), 7.24-7.29 (2H, m), 7.44-7.56 (3H, m), 8.43 (1H, d, J=8.8 Hz), 8.55 (3H, s).

Example 163

(E)-3-[3-(Aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenamide hydrochloride

(1) To a solution of 4-butoxy-3-[(tert-butoxycarbonyl)amino]methyl-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid (4.60 g, 10 mmol) and N-methylmorpholine (1.3 mL, 12 mmol) in tetrahydrofuran (30 mL) was added ethyl chloroformate (1.2 mL, 12 mmol) at 0°C and the mixture was stirred at 10 0°C for 10 min. To the obtained mixture were added sodium tetrahydronate (1.13 g, 30 mmol) and methanol (5 mL), and the mixture was stirred at 0°C for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The precipitated crystals were recrystallized from ethyl acetate - diisopropyl ether to give tert-butyl (4-butoxy-6-hydroxymethyl-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (2.89 g, 64.8%) as crystals.

Melting point 92-93°C.

Elemental analysis for C₂₅H₃₈N₂O₅

Calculated: C, 67.24; H, 8.58; N, 6.27.

Found: C, 67.09; H, 8.43; N, 6.25.

(2) ¹H-NMR(CDCl₃) δ: 0.98 (9H, s), 1.01 (3H, t, J=7.4 Hz), 1.46-1.63 (11H, m), 1.77-1.92 (2H, m), 2.80 (1H, bs), 3.85 (2H, t, J=6.8 Hz), 4.14 (2H, bs), 4.56 (2H, d, J=5.0 Hz), 4.82 (2H, s), 5.15 (1H, bs), 7.42 (1H, d, J=8.4 Hz), 7.53 (1H, s), 8.19 (1H, d, J=8.4 Hz).

(2) To a solution of tert-butyl (4-butoxy-2-cyclopropylmethyl-6-formyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (2.27 g, 6.2 mmol) in tetrahydrofuran (30 mL) was added manganese dioxide (8.1 g) and the mixture was stirred at room temperature for 12 h. Manganese dioxide was filtered off and the mother liquor was concentrated under reduced pressure. The

residue was purified by silica gel column chromatography to give tert-butyl (4-butoxy-6-formyl-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (2.52 g, 91.6%) as crystals.

5 Melting point 149-150°C.

Elemental analysis for $C_{25}H_{38}N_2O_5$ 0.25H₂O

Calculated: C, 66.87; H, 8.19; N, 6.24.

Found: C, 67.09; H, 8.15; N, 6.05.

¹H-NMR(CDCl₃) δ: 1.01 (9H, s), 1.06 (3H, t, J=7.4 Hz),

10 1.45 (9H, s), 1.52-1.71 (2H, m), 1.84-1.98 (2H, m), 3.91 (2H, t, J=6.4 Hz), 4.18 (2H, bs), 4.61 (2H, d, J=5.4 Hz), 4.72 (1H, bs), 7.96 (1H, dd, J=1.7, 8.4 Hz), 7.53 (1H, d, J=1.7 Hz), 8.55 (1H, d, J=8.4 Hz), 10.19 (1H, s).

(3) To a solution of ethyl diethylphosphonoacetate (1.1 mL, 5.5 mmol) in N,N-dimethylformamide (30 mL) was added sodium hydride (0.22 g, 5.5 mmol) (60% in oil), and the mixture was stirred at room temperature for 10 min. To the obtained mixture was added a solution of tert-butyl (4-butoxy-6-formyl-2-neopentyl-1-oxo-1,2-dihydro-3-

20 isoquinolinyl)methylcarbamate (2.45 g, 5.5 mmol) in N,N-dimethylformamide (10 mL) and the mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous

25 magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give ethyl (E)-3-[4-butoxy-3-[(tert-butoxycarbonyl)amino]methyl]-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenate (2.03 g, 71.7%) as

30 an amorphous.

¹H-NMR(CDCl₃) δ: 1.00 (9H, s), 1.06 (3H, t, J=7.4 Hz), 1.37 (3H, t, J=7.2 Hz), 1.45 (9H, s), 1.51-1.66 (2H, m), 1.82-1.93 (2H, m), 3.88 (2H, t, J=6.6 Hz), 4.14 (2H, bs), 4.30 (2H, q, J=7.2 Hz), 4.58 (2H, d, J=5.2 Hz), 4.71 (1H,

35 bs), 6.58 (1H, d, J=16.2 Hz), 7.65 (1H, dd, J=1.6, 8.4 Hz), 7.77 (1H, d, J=1.6 Hz), 7.79 (1H, d, J=16.2 Hz),

8.39 (1H, d, J=8.4 Hz).

(4) To a solution of ethyl (E)-3-[4-butoxy-3-[(tert-butoxycarbonyl)amino]methyl]-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenate (0.67g, 1.3 mmol)

5 in tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N sodium hydroxide (3 mL). The obtained mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The
10 extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - n-hexane to give (E)-3-[4-butoxy-3-[(tert-butoxycarbonyl)amino]methyl]-2-neopentyl-1-oxo-
15 1,2-dihydro-6-isoquinolinyl]-2-propenic acid (0.53 g, 84.1%) as crystals.

Melting point 138-139°C.

Elemental analysis for C₂₇H₃₈N₂O₆

Calculated: C, 66.64; H, 7.87; N, 5.76.

20 Found: C, 66.57; H, 7.84; N, 5.57.

¹H-NMR(CDCl₃) δ: 0.99 (9H, s), 1.07 (3H, t, J=7.3 Hz), 1.48 (9H, s), 1.49-1.67 (2H, m), 1.83-1.94 (2H, m), 3.88 (2H, t, J=6.6 Hz), 4.14 (2H, bs), 4.59 (2H, d, J=4.8 Hz), 5.32 (1H, bs), 6.57 (1H, d, J=15.7 Hz), 7.58 (1H, d,
25 J=8.5 Hz), 7.68 (1H, s), 7.83 (1H, d, J=15.7 Hz), 8.29 (1H, d, J=8.5 Hz).

(5) A solution of (E)-3-[4-butoxy-3-[(tert-butoxycarbonyl)amino]methyl]-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenic acid (0.34 g, 0.7 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

30 hydrochloride (0.27 g, 1.4 mmol) and 1-hydroxybenzotriazole ammonium salt (0.21 g, 1.4 mmol) in N,N-dimethylformamide (10 mL) was stirred at room temperature for 2 h. The reaction mixture was poured
35 into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous

magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give (E)-3-[4-butoxy-3-[(tert-butoxycarbonyl)amino]methyl]-2-

5 neopentyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenamide (0.29 g, 87.9%) as crystals.

Melting point 121-122°C.

Elemental analysis for $C_{27}H_{39}N_3O_5$ 0.5H₂O

Calculated: C, 65.56; H, 8.15; N, 8.50.

10 Found: C, 66.18; H, 8.06; N, 8.59.

¹H-NMR(CDCl₃) δ: 0.99 (9H, s), 1.05 (3H, t, J=7.2 Hz), 1.46 (9H, s), 1.53-1.65 (2H, m), 1.83-1.93 (2H, m), 3.88 (2H, t, J=6.5 Hz), 4.18 (2H, bs), 4.58 (2H, d, J=4.8 Hz), 4.92 (1H, bs), 5.74 (1H, bs), 5.91 (1H, bs), 6.60 (1H, d, J=15.6 Hz), 7.58 (1H, dd, J=1.5, 8.4 Hz); 7.73 (1H, d, J=1.5 Hz), 7.75 (1H, d, J=15.6 Hz), 8.31 (1H, d, J=8.4 Hz).

(6) To a solution of (E)-3-[4-butoxy-3-[(tert-butoxycarbonyl)amino]methyl]-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenamide (0.24 g, 0.5 mmol) in ethyl acetate (5 mL) was added a solution of 4N hydrogen chloride in ethyl acetate (5 mL) and the obtained solution was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the precipitated crystals were recrystallized from methanol - diethyl ether to give (E)-3-[3-(aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenamide hydrochloride (0.19 g, 90.5%) as crystals.

30 Melting point 187-188°C.

Elemental analysis for $C_{22}H_{32}N_3O_3Cl$ 0.75H₂O

Calculated: C, 60.68; H, 7.75; N, 9.65.

Found: C, 60.53; H, 7.74; N, 9.73.

¹H-NMR(DMSO-d₆) δ: 0.91 (9H, s), 1.01 (3H, t, J=7.3 Hz), 1.52-1.63 (2H, m), 1.82-1.93 (2H, m), 3.96 (2H, t, J=6.3 Hz), 4.12 (2H, bs), 4.24 (2H, bs), 4.91 (1H, bs), 6.84

(1H, d, J=15.8 Hz), 7.29 (1H, bs), 7.63 (1H, d, J=15.8 Hz), 7.81 (1H, d, J=8.4 Hz), 7.87 (1H, bs), 8.29 (1H, d, J=8.4 Hz), 8.58 (3H, bs).

Example 164

- 5 2-[(3-(Aminomethyl)-2-isobutyl-1-oxo-4-(4,4,4-trifluorobutoxy)-1,2-dihydro-6-isoquinolinyl]oxy]acetamide hydrochloride
(1) A solution of 4-benzyloxyphthalic anhydride (4.07 g, 16 mmol) and ethyl 2-(isobutylamino)acetate (2.86 g, 18 mmol) in tetrahydrofuran (30 mL) was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in N,N-dimethylformamide (30 mL), and potassium carbonate (2.21 g, 16 mmol) and ethyl iodide (1.5 mL, 19.2 mmol) were added thereto. The mixture was stirred at room temperature for 3 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in ethanol (50 mL), and a solution (10.9 g, 32 mmol) of 20% sodium ethoxide in ethanol was added thereto. The mixture was stirred at room temperature for 1 h. The reaction mixture was poured into 1N hydrochloric acid (70 mL) and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography and the component eluted earlier was concentrated to give ethyl 7-benzyloxy-4-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (4.21 g, 66.6%) as an oil.
- 35 $^1\text{H-NMR}(\text{CDCl}_3)$ δ : 0.82 (6H, d, J=6.6 Hz), 1.45 (3H, t, J=7.1 Hz), 1.77-1.91 (1H, m), 4.42-4.52 (4H, m), 7.31-

7.58 (6H, s), 7.97 (1H, d, J=2.6 Hz), 8.10 (1H, d, J=8.8 Hz), 11.45 (1H, s).

The component eluted later was concentrated to give ethyl 6-benzyloxy-4-hydroxy-2-isobutyl-1-oxo-1,2-

⁵ dihydro-3-isoquinolinecarboxylate (0.80 g, 12.7%) as crystals.

Melting point 92-93°C.

Elemental analysis for C₂₃H₂₅NO₅

Calculated: C, 69.86; H, 6.37; N, 3.54.

¹⁰ Found: C, 69.68; H, 6.20; N, 3.51.

¹H-NMR(CDCl₃) δ: 0.81 (6H, d, J=6.6 Hz), 1.46 (3H, t, J=7.2 Hz), 1.73-1.87 (1H, m), 4.39 (2H, d, J=7.2 Hz), 4.48 (2H, q, J=7.2 Hz), 5.21 (2H, s), 7.28-7.49 (6H, m), 7.60 (1H, d, J=2.6 Hz), 8.38 (1H, d, J=8.8 Hz), 11.23.

¹⁵ (1H, s).

(2) To a solution of ethyl 6-benzyloxy-4-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (5.93 g, 15 mmol), 4,4,4-trifluorobutanol (2.31 g, 18 mmol) and tributylphosphine (7.5 mL, 30 mmol) in

²⁰ tetrahydrofuran (50 mL) was added 1,1'-(azodicarbonyl)dipiperidine (7.57 g, 30 mmol) and the mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column

²⁵ chromatography to give ethyl 6-benzyloxy-2-isobutyl-1-oxo-4-(4,4,4-trifluorobutoxy)-1,2-dihydro-3-isoquinolinecarboxylate (6.71 g, 88.5%) as an oil.

¹H-NMR(CDCl₃) δ: 0.89 (6H, d, J=6.6 Hz), 1.43 (3H, t, J=7.2 Hz), 1.90-2.37 (5H, m), 3.83-3.92 (4H, m), 4.43

³⁰ (2H, q, J=7.2 Hz), 5.22 (2H, s), 7.03 (1H, d, J=2.4 Hz), 7.21 (1H, dd, J=2.4, 9.0 Hz), 7.33-7.46 (5H, m), 8.37 (1H, d, J=9.0 Hz).

(3) To a solution of ethyl 6-benzyloxy-2-isobutyl-1-oxo-4-(4,4,4-trifluorobutoxy)-1,2-dihydro-3-

³⁵ isoquinolinecarboxylate (6.57 g, 13 mmol) in ethanol (50 mL) was added an aqueous solution (20 mL) of sodium

hydroxide (2.08 g, 52 mmol). The obtained mixture was refluxed under heating for 12 h. The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was
5 washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - n-hexane to give 6-benzyloxy-2-isobutyl-1-oxo-4-(4,4,4-trifluorobutoxy)-1,2-dihydro-3-
10 isoquinolinecarboxylic acid (4.89 g, 78.7%) as crystals. Melting point 130-131°C.
 $^1\text{H-NMR}(\text{CDCl}_3)$ δ : 0.85 (6H, d, $J=6.4$ Hz), 1.92-2.39 (5H, m), 3.89-3.93 (4H, m), 5.16 (2H, s), 6.79 (1H, d, $J=2.6$ Hz), 7.71 (1H, dd, $J=2.6$, 8.8 Hz), 7.32-7.41 (5H, m),
15 8.18 (1H, d, $J=8.8$ Hz).
(4) 6-Benzyl-2-isobutyl-1-oxo-4-(4,4,4-trifluorobutoxy)-1,2-dihydro-3-isoquinolinecarboxylic acid (4.77 g, 10 mmol) was dissolved in tetrahydrofuran (50 mL), and oxalyl chloride (1.1 mL, 12 mmol) and N,N-dimethylformamide (3 drops) were added. The mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in tetrahydrofuran (20 mL). The obtained solution was added dropwise to a suspension of
20 sodium tetrahydroborate (1.32 g, 35 mmol) in 1,2-dimethoxyethane (50 mL) at 0°C. The obtained mixture was stirred at 0°C for 1 h. The reaction mixture was poured into 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over
25 anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - n-hexane to give 6-benzyloxy-3-hydroxymethyl-2-isobutyl-4-(4,4,4-trifluorobutoxy)-1(2H)-isoquinolinone (4.02 g, 84.6%) as
30 crystals.
35 Melting point 112-113°C.

Elemental analysis for C₂₅H₂₈NO₄F₃

Calculated: C, 65.67; H, 5.94; N, 2.95.

Found: C, 65.77; H, 6.21; N, 3.03.

¹H-NMR(CDCl₃) δ: 0.91 (6H, d, J=6.6 Hz), 1.97-2.43 (5H, m), 2.56 (1H, bs), 3.83 (2H, t, J=6.2 Hz), 4.03 (2H, d, J=7.4 Hz), 4.76 (2H, d, J=5.6 Hz), 5.20 (2H, s), 6.94 (1H, d, J=2.2 Hz), 7.12 (1H, dd, J=2.2, 8.8 Hz), 7.30-7.45 (5H, m), 8.27 (1H, d, J=8.8 Hz).

(5) To a solution of 6-benzyloxy-3-hydroxymethyl-2-isobutyl-4-(4,4,4-trifluorobutoxy)-1(2H)-isoquinolinone (3.80 g, 8 mmol) in toluene (30 mL) was added thionyl chloride (1.2 mL, 16 mmol). The obtained mixture was refluxed under heating for 2 h. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 6-benzyloxy-3-chloromethyl-2-isobutyl-4-(4,4,4-trifluorobutoxy)-1(2H)-isoquinolinone (3.42 g, 88.8%) as an oil.

¹H-NMR(CDCl₃) δ: 0.95 (6H, d, J=6.6 Hz), 2.00-2.46 (5H, m), 3.91 (2H, t, J=6.2 Hz), 4.04 (2H, d, J=7.6 Hz), 4.76 (2H, s), 5.23 (2H, s), 7.02 (1H, d, J=2.6 Hz), 7.12-7.46 (6H, m), 8.38 (1H, d, J=8.8 Hz).

(6) A solution of 6-benzyloxy-3-chloromethyl-2-isobutyl-4-(4,4,4-trifluorobutoxy)-1(2H)-isoquinolinone (3.37 g, 7 mmol) and potassium phthalimide (1.94 g, 10.5 mmol) in N,N-dimethylformamide (30 mL) was stirred at room temperature for 6 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, and the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - n-hexane to give 2-[[6-benzyloxy-2-isobutyl-1-oxo-4-(4,4,4-trifluorobutoxy)-1,2-dihydro-3-isoquinolinyl]methyl]-1H-

isoindole-1,3(2H)-dione (3.91 g, 94.4%) as crystals.

Melting point 131-132°C.

Elemental analysis for C₃₃H₃₁N₂O₅F₃

Calculated: C, 66.88; H, 5.27; N, 4.73.

⁵ Found: C, 67.25; H, 5.21; N, 4.84.

¹H-NMR(CDCl₃) δ: 0.95 (6H, d, J=6.6 Hz), 1.95-2.40 (5H, m), 3.93 (2H, t, J=6.4 Hz), 4.05 (2H, d, J=7.8 Hz), 4.97 (2H, s), 5.21 (2H, s), 6.98 (1H, d, J=2.6 Hz), 7.16 (1H, dd, J=2.6, 8.8 Hz), 7.28-7.45 (5H, m), 7.68-7.87 (4H, m), 10 8.35 (1H, d, J=8.8 Hz).

(7) To a solution of 2-[[6-benzyloxy-2-isobutyl-1-oxo-4-(4,4,4-trifluorobutoxy)-1,2-dihydro-3-isoquinolinyl]methyl]-1H-isoindole-1,3(2H)-dione (3.85 g, 6.5 mmol) in ethanol (30 mL) was added hydrazine

¹⁵ monohydrate (0.95 mL, 19.5 mmol). The obtained mixture was refluxed under heating for 2 h. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over ²⁰ anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (30 mL) and di-t-butyl dicarbonate (2.2 mL, 9.8 mmol) was added thereto. The obtained mixture was stirred at room temperature for 1 h. The reaction ²⁵ mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give tert-butyl [6-benzyloxy-2-isobutyl-1-oxo-4-(4,4,4-trifluorobutoxy)-1,2-dihydro-3-isoquinolinyl]-

³⁰ methylcarbamate (0.36 g, 87.8%) as crystals.

Melting point 117-118°C.

Elemental analysis for C₃₂H₃₇N₂O₅F₃

³⁵ Calculated: C, 64.04; H, 6.63; N, 4.98.

Found: C, 64.33; H, 6.75; N, 5.00.

¹H-NMR(CDCl₃) δ: 0.94 (6H, d, J=7.0 Hz), 1.46 (9H, s), 1.98-2.44 (5H, m), 3.78 (2H, t, J=6.2 Hz), 3.93 (2H, d, J=7.8 Hz), 4.46 (2H, d, J=5.2 Hz), 4.72 (1H, bs), 5.22 (2H, s), 6.97 (1H, d, J=2.4 Hz), 7.16 (1H, dd, J=2.4, 5 9.0 Hz), 7.31-7.46 (5H, m), 8.34 (1H, d, J=9.0 Hz).

(8) A suspension of tert-butyl [6-benzyloxy-2-isobutyl-1-oxo-4-(4,4,4-trifluorobutoxy)-1,2-dihydro-3-isoquinolinyl]methylcarbamate (3.09 g, 5.5 mmol) and 5% palladium carbon (1.0 g) in tetrahydrofuran (20 mL) and 10 ethanol (20 mL) was stirred under a hydrogen atmosphere at room temperature for 2 h. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [6-hydroxy-2-isobutyl-1-oxo-4-(4,4,4-trifluorobutoxy)-1,2-dihydro-3-isoquinolinyl]methylcarbamate (2.48 g, 95.4%) as crystals.

Melting point 173-174°C.

Elemental analysis for C₂₃H₃₁N₂O₅F₃

Calculated: C, 58.47; H, 6.61; N, 5.93.

Found: C, 58.61; H, 6.66; N, 5.84.

¹H-NMR(CDCl₃) δ: 0.95 (6H, d, J=7.0 Hz), 1.47 (9H, s), 2.03-2.45 (5H, m), 3.88 (2H, t, J=5.9 Hz), 3.98 (2H, d, J=7.4 Hz), 4.49 (2H, d, J=4.6 Hz), 4.77 (1H, bs), 7.08-25 7.14 (2H, m), 8.26 (1H, d, J=8.8 Hz), 8.86 (1H, bs).

(9) A solution of tert-butyl [6-hydroxy-2-isobutyl-4-(4,4,4-trifluorobutoxy)-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.47 g, 1 mmol), iodoacetamide (0.27 g, 1.5 mmol) and 1,8-30 diazabicyclo[5.4.0]-7-undecene (0.22 mL, 1.5 mmol) in N,N-dimethylformamide (10 mL) was stirred at 70°C for 12 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and 35 concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give

tert-butyl [6-(2-amino-2-oxoethoxy)-2-isobutyl-4-(4,4,4-trifluorobutoxy)-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.25 g, 48.1%) as crystals.

⁵ Melting point 184-186°C.

Elemental analysis for C₂₅H₃₄N₃O₆F₃

Calculated: C, 56.70; H, 6.47; N, 7.94

Found: C, 56.43; H, 6.55; N, 7.87.

¹H-NMR(CDCl₃) δ: 0.96 (6H, d, J=6.6 Hz), 1.47 (9H, s),

¹⁰ 2.05-2.23 (2H, m), 2.32-2.52 (2H, m), 3.91 (2H, t, J=6.4 Hz), 3.96 (2H, d, J=7.6 Hz), 4.49 (2H, d, J=5.9 Hz), 4.62 (2H, s), 4.74 (1H, bs), 5.81 (1H, bs), 6.54 (1H, bs), 7.00 (1H, d, J=2.6 Hz), 7.10 (1H, dd, J=2.6, 8.8 Hz), 8.38 (1H, d, J=8.8 Hz).

¹⁵ (10) To a solution of tert-butyl [6-(2-amino-2-oxoethoxy)-2-isobutyl-4-(4,4,4-trifluorobutoxy)-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.18 g, 0.35 mmol) in ethyl acetate (5 mL) was added a solution of 4N hydrogen chloride in ethyl acetate (5 mL) and the ²⁰ obtained solution was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the precipitated crystals were recrystallized from methanol - diisopropyl ether to give 2-[[3-(aminomethyl)-2-isobutyl-1-oxo-4-(4,4,4-

²⁵ trifluorobutoxy)-1,2-dihydro-6-isoquinolinyl]oxy]acetamide hydrochloride (0.15 g, 93.8%) as crystals.

Melting point 147-148°C.

Elemental analysis for C₂₀H₂₇N₃O₄ClF₃ H₂O

³⁰ Calculated: C, 49.64; H, 6.04; N, 8.68.

Found: C, 49.73; H, 5.97; N, 8.60.

¹H-NMR(DMSO-d₆) δ: 0.88 (6H, d, J=6.6 Hz), 1.96-2.13 (3H, m), 2.56-2.71 (2H, m), 3.93-4.02 (4H, m), 4.15 (2H, d, J=4.2 Hz), 4.67 (2H, s), 7.05 (1H, d, J=2.4 Hz), 7.24

³⁵ (1H, dd, J=2.4, 8.8 Hz), 7.49 (1H, bs), 7.76 (1H, bs), 8.20 (1H, d, J=8.8 Hz), 8.73 (3H, s).

Example 165

2-[[3-(Aminomethyl)-4-(4-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]oxy]acetamide hydrochloride

(1) A mixed solution of methyl 6-benzyloxy-2-isobutyl-1-oxo-4-trifluoromethanesulfonyloxy-1,2-dihydro-3-isoquinolinecarboxylate (7.70 g, 15 mmol), 4-fluorophenylboronic acid (2.52 g, 18 mmol) and sodium carbonate (3.97 g, 37.5 mmol) in toluene (50 mL), methanol (10 mL) and water (10 mL) was stirred under an argon atmosphere at room temperature for 30 min. To the obtained mixture was added tetrakis(triphenylphosphine)palladium (0.87 g, 0.9 mmol) and the mixture was refluxed under heating under an argon atmosphere for 12 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give methyl 6-benzyloxy-4-(4-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (5.16 g, 74.9%) as crystals.

Melting point 118-119°C.

Elemental analysis for C₂₈H₂₆NO₄F

Calculated: C, 73.19; H, 5.70; N, 3.05.

Found: C, 72.92; H, 5.79; N, 2.97.

¹H-NMR(CDCl₃) δ: 0.92 (6H, d, J=6.6 Hz), 2.02-2.21 (1H, m), 3.49 (3H, s), 3.93 (2H, d, J=7.8 Hz), 4.99 (2H, s), 6.54 (1H, d, J=2.4 Hz), 7.07-7.40 (10H, m), 8.43 (1H, d, J=8.8 Hz).

(2) To a solution of methyl 6-benzyloxy-4-(4-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (5.05 g, 11 mmol) in methanol (30 mL) was added an aqueous solution (10 mL) of lithium hydroxide monohydrate (1.38 g, 33 mmol). The obtained mixture was refluxed under heating for 12 h. The

reaction mixture was poured into water, and, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under

5 reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give 6-benzyloxy-4-(4-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (3.94 g, 80.5%) as crystals.

10 Melting point 236-237°C.

Elemental analysis for C₂₇H₂₄NO₄F

Calculated: C, 72.80; H, 5.43; N, 3.14.

Found: C, 72.41; H, 5.28; N, 3.02.

15 ¹H-NMR(CDCl₃) δ: 0.86 (6H, d, J=6.6 Hz), 2.10-2.24 (1H, m), 3.89 (2H, d, J=7.4 Hz), 4.99 (2H, s), 6.52 (1H, d, J=2.2 Hz), 7.04-7.16 (3H, m), 7.24-7.37 (7H, m), 8.25 (1H, d, J=9.2 Hz).

(3) To a solution of 6-benzyloxy-4-(4-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid

20 (3.79 g, 8.5 mmol) in tetrahydrofuran (30 mL) were added oxalyl chloride (0.9 mL, 10.2 mmol) and N,N-dimethylformamide (3 drops), and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was

25 dissolved in tetrahydrofuran (20 mL). The obtained solution was added dropwise to a suspension of sodium tetrahydroborate (1.13 g, 30 mmol) in 1,2-dimethoxyethane (30 mL) at 0°C. The obtained mixture was stirred at 0°C for 1 h. The reaction mixture was poured

30 into 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 6-benzyloxy-4-(4-

35 fluorophenyl)-3-hydroxymethyl-2-isobutyl-1(2H)-isoquinolinone (3.31 g, 90.2%) as crystals.

Melting point 143-144°C.

Elemental analysis for C₂₇H₂₆NO₃F

Calculated: C, 75.15; H, 6.07; N, 3.25.

Found: C, 75.04; H, 6.28; N, 3.22.

5 ¹H-NMR(CDCl₃) δ: 0.94 (6H, d, J=6.6 Hz), 2.11-2.25 (1H, m), 2.70 (1H, bs), 4.16 (2H, d, J=7.8 Hz), 4.41 (2H, d, J=5.4 Hz), 4.89 (2H, s), 6.28 (1H, d, J=2.4 Hz), 6.93-6.98 (1H, m), 7.13-7.34 (9H, m), 8.20-8.26 (1H, m).

(4) To a suspension of 6-benzyloxy-4-(4-fluorophenyl)-3-hydroxymethyl-2-isobutyl-1(2H)-isoquinolinone (3.24 g, 7.5 mmol) in toluene (50 mL) was added thionyl chloride (1.1 mL, 15 mmol). The obtained mixture was refluxed under heating for 2 h. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 6-benzyloxy-3-chloromethyl-4-(4-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone (3.18 g, 94.4%) as crystals.

¹H-NMR(CDCl₃) δ: 0.99 (6H, d, J=7.0 Hz), 2.13-2.31 (1H, m), 4.14 (2H, d, J=7.6 Hz), 4.35 (2H, s), 4.95 (2H, s), 6.35 (1H, d, J=2.6 Hz), 7.11-7.38 (10H, m), 8.41 (1H, d, J=8.8 Hz).

(5) A solution of 6-benzyloxy-3-chloromethyl-4-(4-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone (3.15 g, 7 mmol) and potassium phthalimide (1.94 g, 10.5 mmol) in N,N-dimethylformamide (100 mL) was stirred at room temperature for 6 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was crystallized from ethyl acetate - diisopropyl ether to give 2-[[6-benzyloxy-4-(4-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methyl]-1H-isoindole-1,3(2H)-

dione (3.42 g, 87.2%) as crystals.

Melting point 198-199°C.

Elemental analysis for $C_{35}H_{29}N_2O_4F$

Calculated: C, 74.98; H, 5.21; N, 5.00.

⁵ Found: C, 74.83; H, 5.01; N, 4.82.

¹H-NMR(CDCl₃) δ: 0.98 (6H, d, J=6.6 Hz), 2.13-2.27 (1H, m), 4.02 (2H, d, J=7.4 Hz), 4.94 (2H, s), 6.31 (1H, d, J=2.6 Hz), 7.02-7.14 (3H, m), 7.20-7.38 (7H, m), 7.66-7.78 (4H, m), 8.39 (1H, d, J=9.2 Hz).

¹⁰ (6) To a solution of 2-[[6-benzyloxy-4-(4-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methyl]-1H-isoindole-1,3(2H)-dione (3.36 g, 6 mmol) in ethanol (30 mL) was added hydrazine monohydrate (0.9 mL, 18 mmol).

The obtained mixture was refluxed under heating for 2 h.

¹⁵ The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in

²⁰ tetrahydrofuran (20 mL) and di-t-butyl dicarbonate (2.1 mL, 9 mmol) was added thereto. The obtained mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over

²⁵ anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give tert-butyl [6-benzyloxy-4-(4-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-

³⁰ isoquinolinyl]methylcarbamate (3.16 g, 99.4%) as crystals.

Melting point 184-185°C.

Elemental analysis for $C_{32}H_{35}N_2O_4F$

Calculated: C, 72.43; H, 6.65; N, 5.28.

³⁵ Found: C, 72.07; H, 6.52; N, 5.18.

¹H-NMR(CDCl₃) δ: 0.98 (6H, d, J=6.6 Hz), 1.42 (9H, s),

2.14-2.27 (1H, m), 4.02 (2H, d, J=6.9 Hz), 4.15 (2H, d, J=5.4 Hz), 4.52 (1H, bs), 4.94 (2H, s), 6.29 (1H, d, J=2.4 Hz), 7.06-7.11 (1H, m), 7.16-7.36 (9H, m), 8.34-8.38 (1H, m).

- 5 (7) A suspension of tert-butyl [6-benzyloxy-4-(4-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (2.65 g, 5 mmol) and 5% palladium carbon (0.8 g) in ethanol (20 mL) and tetrahydrofuran (20 mL) was stirred under a hydrogen atmosphere at room temperature for 2 h. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The obtained crystals were recrystallized from tetrahydrofuran - diisopropyl ether to give tert-butyl [4-(4-fluorophenyl)-6-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (3.11 g, 94.2%) as crystals.

Melting point 229-230°C.

Elemental analysis for C₂₅H₂₉N₂O₄F

- 20 Calculated: C, 68.16; H, 6.64; N, 6.36.
Found: C, 67.98; H, 6.88; N, 6.20.
¹H-NMR(CDCl₃) δ: 0.95 (6H, d, J=6.6 Hz), 1.42 (9H, s), 2.11-2.24 (1H, m), 4.00 (1H, d, J=7.4 Hz), 4.16 (2H, d, J=3.6 Hz), 4.49 (1H, bs), 6.33 (1H, d, J=2.4 Hz), 7.03 (1H, dd, J=2.4, 9.0 Hz), 7.06-7.18 (4H, m), 7.90 (1H, bs), 8.26 (1H, d, J=9.0 Hz).
(8) A solution of tert-butyl [4-(4-fluorophenyl)-6-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.44 g, 1 mmol), 2-iodoacetamide (0.37 g, 2 mmol) and 1,8-diazabicyclo[5.4.0]-7-undecene (0.30 mL, 2 mmol) in N,N-dimethylformamide (10 mL) was stirred at 80°C for 10 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by

silica gel column chromatography to give tert-butyl [6-(2-amino-2-oxoethoxy)-4-(4-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.24 g, 49.0%) as crystals.

⁵ Melting point 218-219°C.

Elemental analysis for C₂₇H₃₂N₃O₅F

Calculated: C, 65.18; H, 6.48; N, 8.45.

Found: C, 64.84; H, 6.75; N, 8.25.

¹H-NMR(CDCl₃) δ: 0.99 (6H, d, J=7.0 Hz), 1.43 (9H, s),

¹⁰ 2.13-2.30 (1H, m), 4.04 (2H, d, J=7.6 Hz), 4.17 (2H, d, J=5.6 Hz), 4.35 (2H, s), 4.54 (1H, bs), 5.75 (1H, bs), 6.28 (1H, d, J=2.5 Hz), 6.49 (1H, bs), 7.04 (1H, dd, J=2.5, 9.0 Hz), 7.21-7.24 (4H, m), 8.42 (1H, d, J=9.0 Hz).

¹⁵ (9) To a solution of tert-butyl [6-(2-amino-2-oxoethoxy)-4-(4-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.20 g, 0.4 mmol) in ethyl acetate (5 mL) was added a solution of 4N hydrogen chloride in ethyl acetate (5 mL) and the

²⁰ obtained solution was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the residue was crystallized from ethyl acetate - diisopropyl ether to give 2-[[3-(aminomethyl)-4-(4-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-

²⁵ isoquinolinyl]oxy]acetamide hydrochloride (0.16 g, 94.1%) as crystals.

Melting point 189-190°C.

Elemental analysis for C₂₂H₂₅N₃O₃FCl

Calculated: C, 65.18; H, 6.48; N, 8.45.

³⁰ Found: C, 64.84; H, 6.75; N, 8.25.

¹H-NMR(DMSO-d₆) δ: 0.91 (6H, d, J=6.6 Hz), 1.99-2.18 (1H, m), 3.84 (2H, bs), 4.04 (2H, d, J=6.6 Hz), 4.38 (2H, s), 6.29 (1H, d, J=2.0 Hz), 7.20 (1H, dd, J=2.0, 9.0 Hz), 7.34 (1H, bs), 7.38-7.43 (4H, m), 7.56 (1H, bs), 8.27

³⁵ (1H, d, J=9.0 Hz), 8.53 (3H, bs).

Example 166

3-(Aminomethyl)-2-isobutyl-6-(5-methyl-1,3,4-oxadiazol-3-yl)-4-phenyl-1(2H)-isoquinolinone

(1) A mixture of methyl 3-[(tert-butoxycarbonyl)amino]methyl-2-isobutyl-1-oxo-4-phenyl-

5 1,2-dihydro-6-isoquinolinecarboxylate (0.24 g, 0.53 mmol), hydrazine monohydrate (0.65 mL, 13.3 mmol) and methanol (6 mL) was stirred in a sealed tube at 75°C. The reaction mixture was concentrated under reduced pressure and to the residue was added methanol - water

10 (1:1, 4 mL) to allow precipitation of a solid. This solid was collected by filtration, washed with water and dried in vacuo to give tert-butyl [6-(hydrazinocarbonyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.23 g, 94%) as

15 a colorless solid.

¹H-NMR(CDCl₃) δ: 1.00 (6H, d, J=7.0 Hz), 1.43 (9H, s), 2.15-2.35 (1H, m), 4.08 (2H, d, J=7.0 Hz), 4.20 (2H, d, J=5.2 Hz), 4.70 (1H, br), 7.20-7.30 (3H, m), 7.45-7.55 (3H, m), 7.69 (1H, d, J=5.4 Hz), 8.43 (1H, d, J=8.6 Hz).

20 (2) A mixture of tert-butyl [6-(hydrazinocarbonyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.23 g, 0.50 mmol), triethyl orthoacetate (2.0 mL, 10.9 mmol) and n-butanol (10 mL) was refluxed under heating for 20 min. To the

25 reaction mixture was added 1,8-diazabicyclo[5.4.0]-7-undecene (0.075 mL, 0.50 mmol) and the mixture was refluxed under heating for 1 h. To this reaction mixture was added acetic acid (0.040 mL, 0.70 mmol) and the mixture was concentrated under reduced pressure.

30 The residue was partitioned between water (10 mL) and ethyl acetate (30 mL), and the organic layer was washed with water (20 mL), dried over anhydrous magnesium sulfate (9 g) and concentrated under reduced pressure. The residue was purified by silica gel column

35 chromatography (n-hexane:ethyl acetate=2:1 (v/v)) to give tert-butyl [2-isobutyl-6-(5-methyl-1,3,4-oxadiazol-

3-yl)-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.22 g, 91%) as a colorless powder.

¹H-NMR(CDCl₃) δ: 1.02 (6H, d, J=7.2 Hz), 1.43 (9H, s), 5 2.15-2.35 (1H, m), 2.57 (3H, s), 4.10 (2H, d, J=7.2 Hz), 4.22 (2H, d, J=5.4 Hz), 4.57 (1H, br), 7.20-7.35 (2H, m), 7.50-7.65 (4H, m), 8.05 (1H, dm, J=8.4 Hz), 8.58 (1H, dd, J=2.8, 8.4 Hz).

(3) To tert-butyl [2-isobutyl-6-(5-methyl-1,3,4-¹⁰ oxadiazol-3-yl)-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.20 g, 0.41 mmol) was added a solution (4 mL) of 4N hydrogen chloride in ethyl acetate and the mixture was stirred at room temperature for 17 h. The reaction mixture was concentrated under ¹⁵ reduced pressure and to the residue was added diisopropyl ether (5 mL). The precipitated powder was collected by filtration. To this powder was added saturated aqueous sodium hydrogencarbonate (30 mL) and the mixture was extracted twice with a solution (25 mL) ²⁰ of ethyl acetate - tetrahydrofuran (1:1). The organic layers were combined and the mixture was washed with saturated brine (25 mL), dried over anhydrous magnesium sulfate (15 g) and concentrated under reduced pressure. The residue was purified by silica gel column ²⁵ chromatography (ethyl acetate:methanol=20:1 (v/v)) and recrystallized from n-hexane - ethyl acetate (5:1) to give the title compound (0.11 g, 72%) as pale-yellow crystals.

Elemental analysis for C₂₃H₂₄N₄O₂,
³⁰ Calculated: C, 71.11; H, 6.23; N, 14.42.
Found: C, 71.09; H, 6.28; N, 14.37.

¹H-NMR(CDCl₃) δ: 1.02 (6H, d, J=6.6 Hz), 2.15-2.40 (1H, m), 2.57 (3H, s), 3.69 (2H, bs), 4.24 (2H, d, J=7.4 Hz), 7.25-7.35 (2H, m), 7.45-7.60 (2H, m), 7.62 (1H, d, J=1.0 Hz), 8.05 (1H, dd, J=1.6, 8.4 Hz), 8.59 (1H, d, J=8.4 Hz).

Melting point 179-181°C

Example 167

6-Acetyl-3-(aminomethyl)-2-isobutyl-4-phenyl-1(2H)-isoquinolinone hydrochloride

- 5 (1) To a mixture of 3-[(tert-butoxycarbonyl)amino]methyl-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinecarboxylic acid (0.81 g, 1.8 mmol), N,O-dimethylhydroxylamine hydrochloride (0.211 g, 2.16 mmol), 1-hydroxy-1H-benzotriazole monohydrate
10 (0.365 g, 2.7 mmol), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (0.517 g, 2.7 mmol) and N,N-dimethylformamide (10 mL) was added triethylamine (0.301 mL, 2.16 mmol), and the mixture was stirred at room temperature for 17 h. The reaction mixture was poured
15 into 0.1 M aqueous citric acid solution (100 mL) and extracted 3 times with ethyl acetate (50 mL). The organic layers were combined, washed once with 0.1 M aqueous citric acid solution (50 mL), twice with saturated aqueous sodium hydrogencarbonate (50 mL) and
20 once with saturated brine (50 mL), dried over anhydrous magnesium sulfate (15 g), and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate=3:4 (v/v)) to give tert-butyl (2-isobutyl-6-
- 25 {[methoxy(methyl)amino]carbonyl}-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinylmethylcarbamate (0.83 g, 94%) as a colorless solid.

¹H-NMR(CDCl₃) δ: 1.02 (6H, d, J=7.0 Hz), 1.43 (9H, s), 2.15-2.35 (1H, m), 3.27 (3H, s), 3.42 (3H, s), 4.09 (2H, d, J=7.2 Hz), 4.21 (2H, d, J=5.4 Hz), 4.43 (1H, br), 7.20-7.30 (3H, m), 7.45-7.55 (3H, m), 7.69 (1H, dd, J=1.6, 8.2 Hz), 8.50 (1H, d, J=8.2 Hz).

(2) Tert-butyl (2-isobutyl-6-[{methoxy(methyl)amino]carbonyl}-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinylmethylcarbamate (0.175 g, 0.355 mmol) was dissolved in tetrahydrofuran (5 mL) and a

solution (0.15 mL, 0.43 mmol) of 3 M methyl magnesium bromide in diethyl ether was added dropwise under ice-cooling. This mixture was stirred at room temperature for 1 h and quenched with saturated aqueous ammonium

- 5 chloride solution (5 mL). The whole was extracted with ethyl acetate (10 mL), and the organic layer was washed once each with 0.1 M aqueous citric acid solution (10 mL), saturated aqueous sodium hydrogencarbonate (10 mL) and saturated brine (10 mL), dried over anhydrous
10 magnesium sulfate (12 g) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate=5:2 (v/v)) to give tert-butyl (6-acetyl-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.132 g, 83%)
15 as a colorless powder.

¹H-NMR(CDCl₃) δ: 1.01 (6H, d, J=7.2 Hz), 1.43 (9H, s), 2.15-2.35 (1H, m), 2.27 (3H, s), 4.10 (2H, d, J=7.2 Hz), 4.23 (2H, d, J=5.4 Hz), 4.49 (1H, br), 7.20-7.30 (2H, m), 7.45-7.65 (4H, m), 7.96 (1H, dd, J=1.8, 8.4 Hz), 8.54 (1H, d, J=8.4 Hz).

(3) Tert-butyl (6-acetyl-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.10 g, 0.22 mmol) was dissolved in ethyl acetate (4 mL) and a solution (1 mL) of 4N hydrogen chloride in ethyl acetate
25 was added thereto. The mixture was stirred at room temperature for 17 h. The reaction mixture was concentrated under reduced pressure and the residue was precipitated from ethyl acetate - diisopropyl ether (1:10) to give the title compound (0.084 g, 98%) as a
30 pale-yellow powder.

Elemental analysis for C₂₂H₂₄N₂O₂ HCl H₂O,

Calculated: C, 65.58; H, 6.75; N, 6.95.

Found: C, 66.25; H, 6.73; N, 6.83.

¹H-NMR(CD₃OD) δ: 1.02 (6H, d, J=6.6 Hz), 2.10-2.30 (1H,
35 m), 2.50 (3H, s), 4.05-4.20 (4H, m), 7.35-7.45 (2H, m), 7.55-7.70 (4H, m), 8.15 (1H, dd, J=1.4, 8.4 Hz), 8.53

(1H, d, J=8.4 Hz).

Melting point 179°C (decomposition)

Example 168

- 3-(Aminomethyl)-2-isobutyl-6-(1,3-oxazol-5-yl)-4-phenyl-
5 1(2H)-isoquinolinone hydrochloride
(1) Tert-Butyl (6-formyl-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.20 g, 0.45 mmol) was dissolved in methanol (10 mL) and p-toluene sulfonylmethylisocyanide (0.088 g, 0.45 mmol) and
10 potassium carbonate (0.125 g, 0.90 mmol) were added. This mixture was refluxed under heating for 30 min and the reaction mixture was partitioned between saturated aqueous sodium hydrogencarbonate (50 mL) and ethyl acetate - tetrahydrofuran (1:1 (v/v), 50 mL). The
15 organic layer was washed once each with saturated aqueous sodium hydrogencarbonate (50 mL) and saturated brine (50 mL), dried over anhydrous magnesium sulfate (12 g) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography
20 (n-hexane:ethyl acetate=2:1 (v/v)) to give tert-butyl [2-isobutyl-6-(1,3-oxazol-5-yl)-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.16 g, 75%) as a colorless solid.
¹H-NMR(CDCl₃) δ: 1.02 (6H, d, J=7.0 Hz), 1.43 (9H, s),
25 2.15-2.40 (1H, m), 4.09 (2H, d, J=7.2 Hz), 4.22 (2H, d, J=5.6 Hz), 4.51 (1H, br), 7.20 (1H, d, J=1.4 Hz), 7.20-7.35 (2H, m), 7.31 (1H, s), 7.45-7.60 (3H, m), 7.70 (1H, dd, J=1.4, 8.4 Hz), 7.86 (1H, s), 8.51 (1H, d, J=8.4 Hz).
(2) Tert-butyl [2-isobutyl-6-(1,3-oxazol-5-yl)-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.14 g, 0.30 mmol) was dissolved in methanol (4 mL) and a solution (10 mL) of 4N hydrogen chloride in ethyl acetate were added thereto. This mixture was stirred at room temperature for 1 h and the precipitated crystals
30 were collected by filtration to give the title compound (0.084 g, 69%) as a colorless powder.

¹H-NMR(DMSO-d₆) δ: 0.93 (6H, d, J=6.6 Hz), 2.10-2.20 (1H, m), 3.80-4.10 (4H, m), 7.16 (1H, d, J=1.6 Hz), 7.40-7.50 (2H, m), 7.55-7.65 (3H, m), 7.95-8.00 (1H, m), 8.30 (3H, br), 8.40 (1H, d, J=8.8 Hz), 8.43 (1H, s).

⁵ Melting point 217°C (decomposition)

Example 169

3-(Aminomethyl)-2-isobutyl-4-phenyl-6-(2H-tetrazol-5-yl)-1(2H)-isoquinolinone hydrochloride

(1) To a solution (30 mL) of tert-butyl (6-cyano-2-

¹⁰ isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinylmethylcarbamate (0.86 g, 2.0 mmol) in toluene were added sodium azide (0.16 g, 2.5 mmol) and triethylamine hydrochloride (0.28 g, 2.5 mmol), and the mixture was stirred at 90°C for 24 h. The reaction

¹⁵ mixture was poured into water (100 mL), acidified with 1N hydrochloric acid and extracted twice with ethyl acetate (50 mL). The extracts were combined and washed with saturated brine (15 mL), dried over anhydrous magnesium sulfate (12 g) and concentrated under reduced pressure. The residue was recrystallized from tetrahydrofuran - diisopropyl ether (1:5) to give tert-butyl [2-isobutyl-1-oxo-4-phenyl-6-(2H-tetrazol-5-yl)-²⁰ 1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.36 g, 37%) as colorless crystals.

²⁵ ¹H-NMR(CDCl₃) δ: 1.00 (6H, d, J=6.6 Hz), 1.45 (9H, s), 2.15-2.35 (1H, m), 4.15 (2H, bd, J=7.4 Hz), 4.22 (2H, bd, J=5.0 Hz), 7.25-7.50 (6H, m), 7.73 (1H, bs), 8.05 (1H, dm, J=8.4 Hz), 8.44 (1H, d, J=8.4 Hz).

(2) Tert-butyl [2-isobutyl-1-oxo-4-phenyl-6-(2H-

³⁰ tetrazol-5-yl)-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.15 g, 0.32 mmol) was dissolved in tetrahydrofuran (4 mL) and a solution (4 mL) of 4N hydrogen chloride in ethyl acetate was added thereto. This mixture was stirred at room temperature

³⁵ for 17 h, and the precipitated crystals were collected by filtration to give the title compound (0.13 g, 97%)

as colorless crystals.

Elemental analysis for C₂₁H₂₂N₆O HCl 0.5H₂O

Calculated:C, 57.60; H, 5.98; N, 19.19.

Found: C, 57.41; H, 5.96; N, 18.73.

⁵ ¹H-NMR(DMSO-d₆) δ: 0.94 (6H, d, J=6.6 Hz), 2.10-2.20 (1H, m), 3.90 (2H, bs), 4.10 (2H, d, J=6.6 Hz), 7.40-7.50 (2H, m), 7.55-7.65 (3H, m), 7.69 (1H, d, J=1.5 Hz), 8.23 (1H, dd, J=1.5, 8.1 Hz), 8.52 (3H, br), 8.54 (1H, d, J=8.1 Hz).

¹⁰ Melting point 218-220°C

Example 170

3-(Aminomethyl)-2-isobutyl-6-(methylsulfanyl)-4-phenyl-1(2H)-isoquinolinone hydrochloride

(1) A mixture of 3-(aminomethyl)-6-bromo-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (0.19 g, 0.50 mmol), sodium thiometoxide (0.043 g, 0.60 mmol) and dimethylsulfide (2 mL) was stirred at 70°C for 2 h. To the reaction mixture was added another sodium thiometoxide (0.043 g, 0.60 mmol), and the resulting mixture was stirred at 70°C for 2 h. The reaction mixture was partitioned between water (100 mL) and ethyl acetate (25 mL) and the aqueous layer was extracted with ethyl acetate (25 mL). The extracts were combined and washed once each with saturated aqueous sodium hydrogencarbonate (25 mL) and saturated brine (25 mL), dried over anhydrous magnesium sulfate (12 g) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate=1:5 (v/v)) to give 3-(aminomethyl)-2-isobutyl-6-(methylsulfanyl)-4-phenyl-1(2H)-isoquinolinone (0.16 g, 88%) as an oil.

¹H-NMR(CDCl₃) δ: 1.00 (6H, d, J=6.6 Hz), 2.15-2.35 (1H, m), 2.32 (3H, s), 3.66 (2H, bs), 4.19 (2H, d, J=7.8 Hz), 6.69 (1H, d, J=1.8 Hz), 7.20-7.30 (3H, m), 7.45-7.55 (3H, m), 8.36 (1H, d, J=8.4 Hz).

³⁵ (2) 3-(Aminomethyl)-2-isobutyl-6-(methylsulfanyl)-4-phenyl-1(2H)-isoquinolinone (0.13 g, 0.37 mmol) was

dissolved in ethyl acetate (3 mL) and a solution (1 mL) of 4N hydrogen chloride in ethyl acetate was added thereto. The mixture was stirred for 5 min and concentrated under reduced pressure. The obtained

5 residue was crystallized from ethyl acetate - diisopropyl ether (1:2) to give the title compound (0.14 g, 95%) as colorless crystals.

Elemental analysis for C₂₁H₂₄N₂OS HCl,
Calculated: C, 64.85; H, 6.48; N, 7.20.

10 Found: C, 64.79; H, 6.55; N, 6.99.

¹H-NMR(DMSO-d₆) δ: 0.91 (6H, d, J=6.6 Hz), 1.95-2.20 (1H, m), 2.34 (3H, s), 3.86 (2H, bs), 4.00-4.15 (2H, m), 6.59 (1H, d, J=1.8 Hz), 7.35-7.65 (6H, m), 8.23 (1H, d, J=8.4 Hz), 8.46 (1H, bs), 8.58 (2H, bs).

15 Melting point 252-255°C

Example 171

2-{{[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]sulfanyl}acetamide

A solution (2 mL) of 2-mercaptopacetamide (0.27 g, 20 3.0 mmol) in N,N-dimethylformamide was ice-cooled under a nitrogen atmosphere and sodium hydride (0.12 g, 3.0 mmol) (60% in oil) was added thereto. The resulting mixture was stirred under ice-cooling for 30 min. To the obtained suspension was added 3-(aminomethyl)-6-bromo-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (1.06 g, 2.74 mmol), and the mixture was stirred at 80°C for 24 h. The reaction mixture was partitioned between water (100 mL) and ethyl acetate (50 mL), and the aqueous layer was extracted twice with ethyl acetate (50 mL). The extracts were combined and washed with saturated brine (20 mL), dried over anhydrous magnesium sulfate (12 g) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:methanol=1:0-10:1 (v/v)) and recrystallized from n-hexane - ethyl acetate (1:1) to give the title compound (0.54 g, 50%) as a colorless powder.

Elemental analysis for C₂₂H₂₅N₃O₂S,

Calculated:C, 66.81; H, 6.37; N, 10.62.

Found: C, 66.40; H, 6.41; N, 10.26.

¹H-NMR(CDCl₃) δ: 0.99 (6H, d, J=6.6 Hz), 2.20-2.30 (1H,
5 m), 3.52 (2H, s), 3.66 (2H, bs), 4.19 (2H, d, J=7.4 Hz),
5.39 (1H, bs), 6.41 (1H, bs), 6.79 (1H, d, J=1.8 Hz),
7.20-7.35 (3H, m), 7.45-7.55 (3H, m), 8.36 (1H, d, J=8.6
Hz).

Melting point 218-220°C

¹⁰ Example 172

3-(Aminomethyl)-2-isobutyl-6-(methylsulfinyl)-4-phenyl-
1(2H)-isoquinolinone

To a mixture of 3-(aminomethyl)-2-isobutyl-6-(methylsulfanyl)-4-phenyl-1(2H)-isoquinolinone (0.18 g;
15 0.52 mmol), conc. sulfuric acid (0.0168 mL, 0.31 mmol), methanol (2 mL) and water (5 mL) was added Oxone® (0.19 g, 0.31 mmol), and the mixture was stirred at room temperature for 30 min. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate (50 mL)
20 and extracted 3 times with ethyl acetate (25 mL). The extracts were combined, washed with saturated brine (10 mL), dried over anhydrous magnesium sulfate (9 g) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:methanol=10:1 (v/v)). The resulting oil was solidified from diisopropyl ether (1 mL) to give the title compound (0.081 g, 42%) as a pale-yellow powder.

Elemental analysis for C₂₁H₂₄N₂O₂S 2H₂O;

Calculated:C, 62.35; H, 6.98; N, 6.93.

30 Found: C, 62.27; H, 6.58; N, 6.36.

¹H-NMR(CDCl₃) δ: 1.01 (6H, d, J=6.6 Hz), 2.20-2.35 (1H, m), 2.66 (3H, s), 3.69 (2H, bs), 4.24 (2H, d, J=7.4 Hz), 7.20-7.35 (3H, m), 7.45-7.55 (3H, m), 7.64 (1H, dd, J=1.8, 8.6 Hz), 8.63 (1H, d, J=8.6 Hz).

35 Melting point 167°C (decomposition)

Example 173

3-(Aminomethyl)-2-isobutyl-6-(methylsulfonyl)-4-phenyl-1(2H)-isoquinolinone hydrochloride

(1) A mixture of tert-butyl (6-bromo-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.24

5 g, 0.5 mmol), sodium thiometoxide (0.080 g, 1.1 mmol) and N,N-dimethylformamide (4 mL) was stirred at 85°C for 1 h, and the reaction mixture was poured into water (50 mL) and extracted twice with ethyl acetate (25 mL). The extracts were combined, washed with saturated aqueous

10 sodium hydrogencarbonate (15 mL) and saturated brine (15 mL), dried over anhydrous magnesium sulfate (12 g) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-

hexane:ethyl acetate=4:1 (v/v)) to give tert-butyl [2-isobutyl-6-(methylsulfanyl)-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.17 g, 73%) as a colorless powder.

¹H-NMR(CDCl₃) δ: 1.00 (6H, d, J=6.6 Hz), 1.43 (9H, s), 2.15-2.35 (1H, m), 2.32 (3H, s), 4.06 (2H, d, J=7.8 Hz), 20 4.19 (2H, d, J=6.0 Hz), 4.46 (1H, br), 6.68 (1H, d, J=1.8 Hz), 7.20-7.35 (3H, m), 7.40-7.60 (3H, m), 8.34 (1H, d, J=8.4 Hz).

(2) To a solution (5 mL) of tert-butyl [2-isobutyl-6-(methylsulfanyl)-1-oxo-4-phenyl-1,2-dihydro-3-

25 isoquinolinyl]methylcarbamate (0.17 g, 0.37 mmol) in dichloromethane was added m-chloroperbenzoic acid (0.13 g, 0.77 mmol) under ice-cooling, and the mixture was stirred at room temperature for 1 h. The reaction mixture was washed once with 5% aqueous sodium

30 thiosulfate solution (15 mL) and twice with saturated aqueous sodium hydrogencarbonate (15 mL), and partitioned using a PTFE tube. The organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-

35 hexane:ethyl acetate=2:1 (v/v)) to give tert-butyl [2-isobutyl-6-(methylsulfonyl)-1-oxo-4-phenyl-1,2-dihydro-

3-isoquinolinyl]methylcarbamate (0.16 g, 93%) as a colorless oil.

¹H-NMR(CDCl₃) δ: 1.01 (6H, d, J=6.6 Hz), 1.43 (9H, s), 2.15-2.35 (1H, m), 2.99 (3H, s), 4.12 (2H, d, J=6.9 Hz),
⁵ 4.24 (2H, d, J=6.0 Hz), 4.42 (1H, br), 7.30-7.35 (2H, m), 7.50-7.60 (4H, m), 7.94 (1H, dd, J=1.8, 8.4 Hz), 8.66 (1H, d, J=8.4 Hz).

(3) A mixture of tert-butyl [2-isobutyl-6-(methylsulfonyl)-1-oxo-4-phenyl-1,2-dihydro-3-
¹⁰ isoquinolinyl]methylcarbamate (0.16 g, 0.33 mmol) and a solution (5 mL) of 4N hydrogen chloride in ethyl acetate was stirred for 1 h and concentrated under reduced pressure. The obtained residue was precipitated from ethyl acetate - diisopropyl ether (1:10) to give the
¹⁵ title compound (0.12 g, 87%) as a colorless powder.

Elemental analysis for C₂₁H₂₄N₂O₃S HCl H₂O 0.25IPE,
Calculated:C, 58.18; H, 6.62; N, 6.03.
Found: C, 58.15; H, 6.87; N, 5.89.

¹H-NMR(DMSO-d₆) δ: 0.93 (6H, d, J=6.6 Hz), 2.05-2.20 (1H,
²⁰ m), 3.22 (3H, s), 3.90 (2H, bs), 4.11 (2H, bd, J=6.6 Hz), 7.40-7.50 (3H, m), 7.55-7.70 (3H, m), 8.09 (1H, dd,
J=1.8, 8.4 Hz), 8.57 (1H, d, J=8.4 Hz), 8.60 (1H, br).
Melting point 209°C (decomposition)

Example 174

²⁵ 3-(Aminomethyl)-2-isobutyl-6-(methanesulfonylamino)-4-phenyl-1(2H)-isoquinolinone hydrochloride

This compound was synthesized according to the method similar to that in Example 88 from 6-amino-3-(tert-butoxycarbonylaminomethyl)-2-isobutyl-4-phenyl-
³⁰ 1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 111 (1)).

¹H-NMR(DMSO-d₆) δ: 0.91 (6H, d, J=6.6 Hz), 2.08 (1H, m), 2.98 (3H, s), 3.85 (2H, s), 4.03 (2H, d, J=6.2Hz), 6.75 (1H, d, J=1.8Hz), 7.36-7.44 (3H, m), 7.54-7.58 (3H, m),
³⁵ 7.77 (1H, d, J=8.8Hz), 8.46 (3H, bs), 10.29 (1H, bs).

Example 175

3-(Aminomethyl)-2-isobutyl-6-(methoxycarbonylamino)-4-phenyl-1(2H)-isoquinolinone hydrochloride

This compound was synthesized according to the method similar to that in Example 88 from 6-amino-3-

⁵ (tert-butoxycarbonylaminomethyl)-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 111 (1)).

¹⁰ $^1\text{H-NMR}(\text{DMSO-d}_6)$ δ : 0.91 (6H, d, $J=6.6$ Hz), 2.08 (1H, m), 3.59 (3H, s), 3.85 (2H, s), 4.02 (2H, d, $J=6.6$ Hz), 7.22

¹⁵ (1H, d, $J=1.8$ Hz), 7.34-7.38 (2H, m), 7.54-7.63 (5H, m), 8.23 (1H, d, $J=8.8$ Hz), 8.40 (3H, bs), 10.04 (1H, s).

Example 176

3-(Aminomethyl)-2-isobutyl-6-(dimethanesulfonylamino)-4-phenyl-1(2H)-isoquinolinone hydrochloride

¹⁵ This compound was synthesized according to the method similar to that in Example 88 from 6-amino-3-(tert-butoxycarbonylaminomethyl)-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 111 (1)).

²⁰ $^1\text{H-NMR}(\text{DMSO-d}_6)$ δ : 0.93 (6H, d, $J=6.6$ Hz), 2.11 (1H, m), 3.34 (3H, s), 3.44 (2H, s), 3.90 (2H, s), 4.08 (2H, d, $J=7.4$ Hz), 6.86 (1H, d, $J=1.8$ Hz), 7.41-7.45 (2H, m), 7.57-7.60 (3H, m), 7.73 (1H, dd, $J=8.4$, 1.8 Hz), 8.43 (1H, d, $J=8.4$ Hz), 8.44 (3H, bs).

²⁵ **Example 177**

N-{3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl}-N'-methylurea hydrochloride.

This compound was synthesized according to the method similar to that in Example 80 from 3-(tert-

³⁰ butoxycarbonylaminomethyl)-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxylic acid (synthesized according to the method similar to that in Example 108 (1)).

$^1\text{H-NMR}(\text{DMSO-d}_6)$ δ : 0.90 (6H, d, $J=6.6$ Hz), 2.07 (1H, m), 2.56 (3H, s), 3.81 (2H, s), 4.00 (2H, d, $J=7.0$ Hz), 6.17

³⁵ (1H, bs), 6.98 (1H, d, $J=2.0$ Hz), 7.34-7.38 (2H, m), 7.54-7.67 (4H, m), 8.17 (1H, d, $J=8.8$ Hz), 8.39 (3H, bs),

9.13 (1H, s).

Example 178

N-[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-N',N'-dimethylurea

5 hydrochloride

This compound was synthesized according to the method similar to that in Example 80 from 3-(tert-butoxycarbonylaminomethyl)-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxylic acid (synthesized according

10 to the method similar to that in Example 108 (1)).

¹H-NMR(DMSO-d₆) δ: 0.91 (6H, d, J=6.6 Hz), 2.07 (1H, m), 2.86 (6H, s), 3.81 (2H, s), 4.02 (2H, d, J=7.0Hz), 7.13 (1H, s), 7.34-7.38 (2H, m), 7.54-7.57 (3H, m), 7.69 (1H, d, J=8.8Hz), 8.17 (1H, d, J=8.8Hz), 8.41 (3H, bs), 8.68

15 (1H, s).

Example 179

N-[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]urea hydrochloride

This compound was synthesized according to the method similar to that in Example 80 from 3-(tert-butoxycarbonylaminomethyl)-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxylic acid (synthesized according

20 to the method similar to that in Example 108 (1)).

¹H-NMR(DMSO-d₆) δ: 0.91 (6H, d, J=6.6 Hz), 2.07 (1H, m), 3.82 (2H, d, J=4.0Hz), 4.02 (2H, d, J=7.2Hz), 5.96 (1H, bs), 6.70 (1H, bs), 6.51 (1H, d, J=1.8Hz), 7.35-7.39 (2H, m), 7.51-7.59 (3H, m), 7.79 (1H, dd, J=8.8, 1.8Hz), 8.18 (1H, d, J=8.8Hz), 8.44 (3H, bs), 9.10 (1H, s).

Example 180

30 (E)-3-[3-(Aminomethyl)-4-(4-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenamide hydrochloride

(1) To a solution of tert-butyl [4-(4-fluorophenyl)-6-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-

35 isoquinolinyl]methylcarbamate (2.00 g, 3.5 mmol) in N,N-dimethylformamide (30 ml) was added sodium hydride (0.19

g, 4.8 mmol) (60% in oil) at 0°C, and the mixture was stirred at 0°C for 10 min. To the obtained mixture was added N-phenyltrifluoromethanesulfonimide (1.71 g, 4.8 mmol) and the mixture was stirred at room temperature 5 for 3 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column 10 chromatography to give tert-butyl [4-(4-fluorophenyl)-2-isobutyl-1-oxo-6-trifluoromethanesulfonyloxy-1,2-dihydro-3-isoquinolinyl]methylcarbamate (2.02 g, 88.2%) as an oil.

¹H-NMR(CDCl₃) δ: 0.99 (6H, d, J=6.6 Hz), 1.43 (9H, s), 15 2.14-2.28 (1H, m), 4.07 (2H, d, J=7.6 Hz), 4.22 (2H, d, J=5.8 Hz), 4.47 (1H, bs), 6.80 (1H, d, J=2.4 Hz), 7.22-7.44 (5H, m), 8.55 (1H, d, J=8.6 Hz).

(2) A suspension of tert-butyl [4-(4-fluorophenyl)-2-isobutyl-1-oxo-6-trifluoromethanesulfonyloxy-1,2-dihydro-3-isoquinolinyl]methylcarbamate (2.00 g, 3.5 mmol), butyl acrylate (0.76 ml, 5.3 mmol), sodium hydrogencarbonate (0.45 g, 5.5 mmol), tetrabutylammonium chloride (0.11 g, 0.4 mmol) and palladium acetate (90 mg, 0.4 mmol) in N,N-dimethylformamide (30 ml) was stirred 20 with heating at 100°C under an argon atmosphere for 24 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column 25 chromatography to give butyl (E)-3-[3-[(tert-butoxycarbonyl)amino]methyl]-4-(4-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenate as an amorphous.

30 35 ¹H-NMR(CDCl₃) δ: 0.95 (3H, t, J=7.7 Hz), 1.00 (6H, d, J=6.6 Hz), 1.34-1.47 (11H, m), 1.62-1.72 (2H, m), 2.18-

2.28 (1H, m), 4.06 (2H, d, J=7.8 Hz), 4.13-4.21 (4H, m),
4.50 (1H, bs), 6.39 (1H, d, J=16.5 Hz), 6.98 (1H, d,
J=1.6 Hz), 7.19-7.27 (4H, m), 7.55 (1H, d, J=16.5 Hz),
7.62 (1H, dd, J=1.6, 8.7 Hz), 8.44 (1H, d, J=8.7 Hz).

⁵ (3) To a solution of butyl (E)-3-[3-[(tert-butoxycarbonyl)amino]methyl]-4-(4-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenate (0.56 g, 1 mmol) in tetrahydrofuran (10 ml) and methanol (10 ml) was added 1N sodium hydroxide (2 ml). The obtained mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give (E)-3-[3-[(tert-butoxycarbonyl)amino]methyl]-4-(4-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenic acid (0.36 g, 72.0%) as crystals.

Melting point 201-202°C.

Elemental analysis for C₂₈H₃₁N₂O₅F 0.25H₂O

Calculated: C, 67.39; H, 6.36; N, 5.61.

Found: C, 67.69; H, 6.27; N, 5.49.

²⁵ ¹H-NMR(CDCl₃) δ: 0.99 (6H, d, J=6.4 Hz), 1.49 (9H, s), 2.11-2.24 (1H, m), 4.04 (2H, d, J=7.2 Hz), 4.13 (2H, d, J=3.0 Hz), 5.74 (1H, bs), 6.28 (1H, d, J=16.4 Hz), 6.77 (1H, s), 7.21-7.34 (5H, m), 7.43 (1H, d, J=16.4 Hz), 8.22 (1H, d, J=8.2 Hz).

³⁰ (4) A solution of (E)-3-[3-[(tert-butoxycarbonyl)amino]methyl]-4-(4-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenic acid (0.20 g, 0.4 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.15 g, 0.8 mmol) and 1-hydroxybenzotriazole ammonium salt (0.12 g, 0.8 mmol) in N,N-dimethylformamide (10 ml) was

stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under

⁵ reduced pressure. The residue was purified by silica gel column chromatography to give (E)-3-[3-[(tert-butoxycarbonyl)amino]methyl]-4-(4-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenamide (0.13 g, 65.0%) as crystals.

¹⁰ Melting point 161-163°C.

¹H-NMR(CDCl₃) δ: 1.00 (6H, d, J=6.6 Hz), 1.44 (9H, s), 2.16-2.24 (1H, m), 4.07 (2H, d, J=7.4 Hz), 4.19 (2H, d, J=5.6 Hz), 4.96 (1H, bs), 5.75 (1H, bs), 6.38 (1H, d, J=15.6 Hz), 6.94 (1H, s), 7.26-7.30 (2H, m), 7.40-7.56

¹⁵ (5H, m), 8.29 (1H, d, J=8.4 Hz).

(5) (E)-3-[3-[(Tert-butoxycarbonyl)amino]methyl]-4-(4-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenamide (0.10 g, 0.2 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the residue was crystallized from ethyl acetate to give (E)-3-[3-(aminomethyl)-4-(4-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenamide hydrochloride

²⁰ (0.08 g, 88.8%) as crystals.

Melting point 255-258°C.

Elemental analysis for C₂₃H₂₅N₃O₂ClF 0.75H₂O

Calculated: C, 62.30; H, 6.02; N, 9.48.

³⁰ Found: C, 61.90; H, 6.38; N, 9.31.

¹H-NMR(DMSO-d₆) δ: 0.92 (6H, d, J=6.6 Hz), 1.99-2.19 (1H, m), 3.86 (2H, d, J=4.0 Hz), 4.08 (2H, d, J=7.0 Hz), 6.57 (1H, d, J=15.8 Hz), 7.00 (1H, d, J=1.6 Hz), 7.18 (1H, bs), 7.32-7.51 (5H, m), 7.67 (1H, bs), 7.78 (1H, dd,

³⁵ J=1.6, 8.4 Hz), 8.35 (1H, d, J=8.4 Hz), 8.61 (3H, bs).

Example 181

2-[[3-(Aminomethyl)-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-6-isoquinolinyl]oxy]acetamide hydrochloride
(1) A mixture of methyl 6-benzyloxy-2-isobutyl-1-oxo-4-trifluoromethanesulfonyloxy-1,2-dihydro-3-

- 5 isoquinolinecarboxylate (9.24 g, 18 mmol), 4-methylphenylboronic acid (2.94 g, 21.6 mmol) and sodium carbonate (2.86 g, 27 mmol) in toluene (50 ml) - methanol (10 ml) - water (10 ml) was stirred under an argon atmosphere at room temperature for 30 min. To the 10 obtained mixture was added tetrakis(triphenylphosphine)palladium (1.04 g, 1 mmol) and the mixture was refluxed under heating under an argon atmosphere for 10 h. The reaction mixture was poured into water and extracted with ethyl acetate.
- 15 After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give methyl 6-benzyloxy-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (6.91 g, 84.4%) as crystals.
- 20 Melting point 142.5-143°C.

Elemental analysis for C₂₉H₂₉NO₄

Calculated: C, 76.46; H, 6.42; N, 3.07.

25 Found: C, 76.35; H, 6.40; N, 2.86.

¹H-NMR(CDCl₃) δ: 0.92 (6H, d, J=6.6 Hz), 2.04-2.20 (1H, m), 2.43 (3H, s), 3.47 (3H, s), 3.93 (2H, d, J=7.6 Hz), 4.97 (2H, s), 6.65 (1H, d, J=2.6 Hz), 7.11-7.37 (10H, m), 8.42 (1H, d, J=8.8 Hz).

- 30 (2) To a suspension of methyl 6-benzyloxy-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (6.83 g, 15 mmol) in methanol (50 ml) was added an aqueous solution (20 ml) of lithium hydroxide monohydrate (1.89 g, 45 mmol). The obtained 35 mixture was refluxed under heating for 24 h. The reaction mixture was poured into water, acidified with

1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from 5 ethyl acetate - diisopropyl ether to give 6-benzyloxy-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (5.78 g, 87.3%) as crystals. Melting point 153-154°C.

¹H-NMR(CDCl₃) δ: 0.85 (6H, d, J=6.6 Hz), 2.03-2.21 (1H, 10 m), 2.42 (3H, s), 3.86 (2H, d, J=7.4 Hz), 4.13 (1H, bs), 4.96 (2H, s), 6.61 (1H, d, J=2.4 Hz), 7.10 (1H, dd, J=2.4, 9.0 Hz), 7.13-7.36 (9H, m), 8.28 (1H, d, J=9.0 Hz).

(3) To a mixed solution of 6-benzyloxy-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (5.74 g, 13 mmol) in tetrahydrofuran (50 ml) were added oxalyl chloride (1.4 ml, 15.6 mmol) and N,N-dimethylformamide (3 drops), and the mixture was stirred at room temperature for 1 h. The reaction mixture was 15 concentrated under reduced pressure and the residue was dissolved in tetrahydrofuran (20 ml). The obtained solution was added dropwise to a suspension of sodium tetrahydroborate (1.72 g, 45.5 mmol) in 1,2-dimethoxyethane (50 ml) at 0°C. The obtained mixture was 20 stirred at 0°C for 1 h. The reaction mixture was poured into 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were 25 recrystallized from ethyl acetate - diisopropyl ether to give 6-benzyloxy-3-hydroxymethyl-2-isobutyl-4-(4-methylphenyl)-1(2H)-isoquinolinone (4.41 g, 79.5%) as crystals.

Melting point 74-76°C.

¹H-NMR(CDCl₃) δ: 0.95 (6H, d, J=6.6 Hz), 2.16-2.26 (1H, 30 m), 2.41 (1H, bs), 2.47 (3H, s), 4.17 (2H, d, J=7.5 Hz),

4.43 (2H, s), 4.89 (2H, s), 6.39 (1H, d, J=2.4 Hz), 6.98 (1H, dd, J=2.4, 8.8 Hz), 7.17 (2H, d, J=7.8 Hz), 7.23-7.34 (7H, m), 8.28 (1H, d, J=8.8 Hz).

(4) To a suspension of 6-benzyloxy-3-hydroxymethyl-2-isobutyl-4-(4-methylphenyl)-1(2H)-isoquinolinone (4.28 g, 10 mmol) in toluene (50 ml) was added thionyl chloride (1.5 ml, 20 mmol). The obtained mixture was refluxed under heating for 2 h. The reaction mixture was poured into saturated aqueous sodium hydrogen carbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 6-benzyloxy-3-chloromethyl-2-isobutyl-4-(4-methylphenyl)-1(2H)-isoquinolinone (4.26 g, 95.5%) as an oil.

¹H-NMR(CDCl₃) δ: 0.99 (6H, d, J=7.0 Hz), 2.14-2.30 (1H, m), 2.47 (3H, s), 4.15 (2H, d, J=6.8 Hz), 4.39 (2H, s), 4.93 (2H, s), 6.45 (1H, d, J=2.6 Hz), 7.09-7.35 (10H, m), 8.40 (1H, d, J=8.8 Hz).

(5) A solution of 6-benzyloxy-3-chloromethyl-2-isobutyl-4-(4-methylphenyl)-1(2H)-isoquinolinone (4.24 g; 9.5 mmol) and potassium phthalimide (2.65 g, 14.3 mmol) in N,N-dimethylformamide (50 ml) was stirred at room temperature for 6 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 2-[6-benzyloxy-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-3-isoquinolinyl]methyl]-1H-isoindole-1,3(2H)-dione (5.07 g, 96.0%) as crystals.

Melting point 158-159°C.

Elemental analysis for C₃₆H₃₂N₂O₄

Calculated: C, 77.68; H, 5.79; N, 5.03.

Found: C, 77.89; H, 5.91; N, 4.96.

¹H-NMR(CDCl₃) δ: 0.98 (6H, d, J=6.6 Hz), 2.14-2.28 (1H, m), 2.38 (3H, s), 4.01 (2H, d, J=7.2 Hz), 4.78 (2H, s), 4.92 (2H, s), 6.41 (1H, d, J=2.6 Hz), 7.09 (1H, dd, J=2.6, 8.8 Hz), 7.12-7.19 (4H, m), 7.20-7.35 (5H, m), 7.66-7.76 (4H, m), 8.38 (1H, d, J=8.8 Hz).

(6) To a suspension of 2-[[6-benzyloxy-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-3-isoquinolinyl]methyl]-1H-isoindole-1,3(2H)-dione (5.01 g, 9 mmol) in ethanol (50 ml) was added hydrazine monohydrate (1.3 ml, 27 mmol). The obtained mixture was refluxed under heating for 1 h. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (50 ml) and di-t-butyl dicarbonate (3.1 ml, 13.5 mmol) was added thereto. The obtained mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give tert-butyl [6-benzyloxy-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (4.48 g, 94.5%) as crystals. Melting point 164-164.5°C.

Elemental analysis for C₃₃H₃₈N₂O₄

Calculated: C, 75.26; H, 7.27; N, 5.32.

Found: C, 75.17; H, 7.39; N, 5.17.

¹H-NMR(CDCl₃) δ: 0.98 (6H, d, J=7.0 Hz), 1.42 (9H, s), 2.13-2.27 (1H, m), 2.46 (3H, s), 4.03 (2H, d, J=7.2 Hz), 4.18 (2H, d, J=5.4 Hz), 4.48 (1H, bs), 4.92 (2H, s), 6.38 (1H, d, J=2.6 Hz), 7.05-7.11 (3H, m), 7.22-7.35 (7H, m), 8.37 (1H, d, J=8.8 Hz).

(7) A suspension of tert-butyl [6-benzyloxy-2-isobutyl-

4-(4-methylphenyl)-1-oxo-1,2-dihydro-3-isoquinolinylmethylcarbamate (4.21 g, 8 mmol) and 5% palladium carbon (2.0 g) in ethanol (20 ml) and tetrahydrofuran (20 ml) was stirred under a hydrogen atmosphere at room temperature for 2 h. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [6-hydroxy-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-3-isoquinolinylmethylcarbamate (3.28 g; 94.0%) as crystals.

Melting point 233-234°C.

Elemental analysis for $C_{26}H_{32}N_2O_4$

Calculated: C, 71.53; H, 7.39; N, 6.42.

Found: C, 71.35; H, 7.35; N, 6.22.

1H -NMR(CDCl₃) δ : 0.96 (6H, d, J=6.6 Hz), 1.41 (9H, s), 2.12-2.26 (1H, m); 2.41 (3H, s), 4.02 (2H, d, J=7.4 Hz), 4.19 (2H, d, J=5.4 Hz), 4.46 (1H, bs), 6.39 (1H, d, J=2.2 Hz), 7.04 (1H, dd, J=2.2, 8.8 Hz), 7.08 (2H, d, J=8.4 Hz), 7.24 (2H, d, J=8.4 Hz), 7.73 (1H, bs), 8.28 (1H, d, J=8.8 Hz).

(8) A solution of tert-butyl [6-hydroxy-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-3-isoquinolinylmethylcarbamate (0.44 g, 1 mmol), 2-iodoacetamide (0.37 g, 2 mmol) and 1,8-diazabicyclo[5.4.0]-7-undecene (0.30 ml, 2 mmol) in N,N-dimethylacetamide (10 ml) was stirred at 80°C for 12 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [6-(2-amino-2-oxoethoxy)-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-3-isoquinolinylmethylcarbamate (0.18 g, 36.7%) as crystals.

Melting point 239-239.5°C.

Elemental analysis for C₂₈H₃₅N₃O₅

Calculated: C, 68.13; H, 7.15; N, 8.51.

Found: C, 67.77; H, 7.09; N, 8.21.

¹H-NMR(CDCl₃) δ: 0.99 (6H, d, J=6.6 Hz), 1.43 (9H, s),

5 2.15-2.29 (1H, m), 2.47 (3H, s), 4.05 (2H, d, J=7.6 Hz),
4.19 (2H, d, J=5.4 Hz), 4.33 (2H, s), 4.48 (1H, bs),
5.69 (1H, bs), 6.34 (1H, d, J=2.6 Hz), 6.52 (1H, bs),
7.04 (1H, dd, J=2.6, 9.0 Hz), 7.10 (2H, d, J=7.9 Hz),
7.31 (2H, d, J=7.9 Hz), 8.42 (1H, d, J=9.0 Hz).

10 (9) Tert-butyl [6-(2-amino-2-oxoethoxy)-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.15 g, 0.3 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the precipitated crystals were recrystallized from ethyl acetate - diisopropyl ether to give 2-[[3-(aminomethyl)-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-6-isoquinolinyl]oxy]acetamide hydrochloride (0.11 g, 91.7%) as crystals.

Melting point 278-280°C.

Elemental analysis for C₂₃H₂₈N₃O₃ 0.5H₂O

Calculated: C, 62.93; H, 6.66; N, 9.57.

25 Found: C, 62.97; H, 6.53; N, 9.28.

¹H-NMR(DMSO-d₆) δ: 0.90 (6H, d, J=6.6 Hz), 1.99-2.16 (1H, m), 2.43 (3H, s), 3.86 (2H, s), 4.04 (2H, d, J=7.0 Hz), 4.36 (2H, s), 6.34 (1H, d, J=2.6 Hz), 7.19 (1H, dd, J=2.6, 8.8 Hz), 7.25 (2H, d, J=8.2 Hz), 7.35 (1H, bs),

30 7.37 (2H, d, J=8.2 Hz), 7.57 (1H, bs), 8.27 (1H, d, J=8.8 Hz), 8.48 (3H, s).

Example 182

3-(Aminomethyl)-2-isobutyl-4-(4-methylphenyl)-1(2H)-isoquinolinone-6-carboxamide hydrochloride

35 (1) To a solution of tert-butyl [6-hydroxy-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-3-

isoquinolinyl]methylcarbamate (Example 181(7)) (2.18 g, 5 mmol) in N,N-dimethylformamide (20 ml) was added sodium hydride (0.30 g, 8.3 mmol) (60% in oil) at 0°C and the mixture was stirred at 0°C for 30 min. To the obtained mixture was added N-phenyltrifluoromethanesulfonimide (2.68 g, 8.3 mmol) and the mixture was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [2-isobutyl-4-(4-methylphenyl)-1-oxo-6-trifluoromethanesulfonyloxy-1,2-dihydro-3-isoquinolinyl]methylcarbamate (2.85 g, 100%) as an oil.
¹H-NMR(CDCl₃) δ: 0.99 (6H, d, J=7.0 Hz), 1.43 (9H, s), 2.14-2.27 (1H, m), 2.47 (3H, s), 4.09 (2H, d, J=7.4 Hz), 4.24 (2H, d, J=5.8 Hz), 4.45 (1H, t, J=2.6 Hz), 6.86 (1H, d, J=2.6 Hz), 7.12 (2H, d, J=8.2 Hz), 7.13-7.40 (3H, m), 8.54 (1H, d, J=8.8 Hz).
(2) A mixture of tert-butyl [2-isobutyl-4-(4-methylphenyl)-1-oxo-6-trifluoromethanesulfonyloxy-1,2-dihydro-3-isoquinolinyl]methylcarbamate (2.84 g, 5 mmol), 1,1'-bis(diphenylphosphino)ferrocene (0.14 g, 0.25 mmol), triethylamine (0.77 ml, 5.5 mmol) and palladium acetate (56 mg, 0.25 mmol) in tetrahydrofuran (20 ml) - methanol (20 ml) was stirred with heating at 100°C under a carbon monoxide atmosphere at 5 atm for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give methyl 3-[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-6-isoquinolinecarboxylate (2.11 g, 88.3%) as crystals.

Melting point 193-194.5°C.

Elemental analysis for C₂₆H₃₄N₂O₅

Calculated: C, 70.27; H, 7.16; N, 5.85.

Found: C, 69.97; H, 7.22; N, 5.71.

⁵ ¹H-NMR(CDCl₃) δ: 1.00 (6H, d, J=6.6 Hz), 1.43 (9H, s), 2.17-2.32 (1H, m), 2.47 (3H, s), 3.86 (3H, s), 4.09 (2H, d, J=7.4 Hz), 4.22 (2H, d, J=5.8 Hz), 4.54 (1H, bs), 7.13 (2H, d, J=7.8 Hz), 7.32 (2H, d, J=7.8 Hz), 7.68 (1H, d, J=1.6 Hz), 8.02 (1H, dd, J=1.6, 8.2 Hz), 8.49 (1H, d, J=8.2 Hz).

(3) To a solution of methyl 3-[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-6-isoquinolinecarboxylate (1.91 g, 4 mmol) in

¹⁵ tetrahydrofuran (10 ml)-methanol (10 ml) was added 1N sodium hydroxide (8 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was ²⁰ washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from tetrahydrofuran - isopropyl ether to give 3-[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid (1.67 g, 90.3%) as crystals.

Melting point 230-231°C.

Elemental analysis for C₂₇H₃₂N₂O₅

Calculated: C, 69.81; H, 6.94; N, 6.03.

³⁰ Found: C, 69.45; H, 7.09; N, 5.67.

¹H-NMR(CDCl₃) δ: 0.98 (6H, d, J=6.6 Hz), 1.49 (9H, s), 2.07-2.25 (1H, m), 2.48 (3H, s), 4.05 (2H, d, J=7.4 Hz), 4.18 (2H, d, J=4.4 Hz), 5.75 (1H, bs), 7.21 (2H, d, J=7.8 Hz), 7.32 (2H, d, J=7.8 Hz), 7.48 (1H, s), 7.79

³⁵ (1H, d, J=8.2 Hz), 8.32 (1H, d, J=8.2 Hz).

(4) A solution of 3-[(tert-

butoxycarbonyl)amino]methyl]-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid (0.92 g, 2 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.77 g, 5 4 mmol) and 1-hydroxybenzotriazole ammonium salt (0.61 g, 4 mmol) in N,N-dimethylformamide (10 ml) was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from tetrahydrofuran - diisopropyl ether to give 3-[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-6-isoquinolinecarboxamide (0.82 g, 89.1%) as crystals. Melting point 225-226°C.

¹H-NMR(CDCl₃) δ: 1.00 (6H, d, J=6.6 Hz), 1.43 (9H, s), 2.17-2.28 (1H, m), 2.46 (3H, s), 4.08 (2H, d, J=7.2 Hz), 4.22 (2H, d, J=5.6 Hz), 4.52 (1H, bs), 5.62 (1H, bs), 6.00 (1H, bs), 7.12 (2H, d, J=7.8 Hz), 7.32 (2H, d, J=7.8 Hz), 7.42 (1H, d, J=1.8 Hz), 7.78 (1H, dd, J=1.8, 8.4 Hz), 8.49 (1H, d, J=8.4 Hz).

(5) A solution of 3-[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-6-isoquinolinecarboxamide (0.42 g, 0.9 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the precipitated crystals were recrystallized from methanol - diethyl ether to give 3-(aminomethyl)-2-isobutyl-4-(4-methylphenyl)-1(2H)-isoquinolinone-6-carboxamide hydrochloride (0.34 g, 94.4%) as crystals.

35 Melting point 286-288°C.

Elemental analysis for C₂₂H₂₆N₃O₃Cl 1.25H₂O

Calculated: C, 62.55; H, 6.80; N, 9.95.

Found: C, 62.66; H, 6.93; N, 9.99.

¹H-NMR(DMSO-d₆) δ: 0.92 (6H, d, J=6.6 Hz), 2.02-2.16 (1H, m), 2.45 (3H, s), 3.88 (2H, s), 4.08 (2H, d, J=7.4 Hz), 5 7.28 (2H, d, J=8.1 Hz), 7.39 (2H, d, J=8.1 Hz), 7.46 (1H, d, J=1.6 Hz), 7.58 (1H, bs), 7.99 (1H, d, J=1.6, 8.2 Hz), 8.16 (1H, bs), 8.36 (1H, d, J=8.2 Hz), 8.49 (3H, bs).

Example 183

3-(Aminomethyl)-2-isobutyl-4-(4-methylphenyl)-1(2H)-

10 isoquinolinone-6-carbonitrile hydrochloride

(1) A solution of 3-[(tert-

butoxycarbonyl)amino]methyl]-2-isobutyl-4-(4-

methylphenyl)-1-oxo-1,2-dihydro-6-

isoquinolinecarboxamide (Example 3 (4)) (0.37 g, 0.8

15 mmol) and cyanuric chloride (0.44 g, 2.4 mmol) in N,N-dimethylformamide (10 mmol) was stirred at 0°C for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated

20 under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [6-cyano-4-(4-methylphenyl)-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.32 g, 91.4%) as crystals.

25 Melting point 156-157°C.

Elemental analysis for C₂₇H₃₁N₃O₃

Calculated: C, 72.78; H, 7.01; N, 9.43.

Found: C, 72.66; H, 7.16; N, 9.46.

¹H-NMR(CDCl₃) δ: 1.00 (6H, d, J=6.6 Hz), 1.43 (9H, s), 30 2.14-2.29 (1H, m), 2.48 (3H, s), 4.09 (2H, d, J=7.6 Hz), 4.24 (2H, d, J=5.8 Hz), 4.45 (1H, bs), 7.10 (2H, d, J=7.7 Hz), 7.31 (1H, d, J=1.4 Hz), 7.35 (2H, d, J=7.7 Hz), 7.63 (1H, dd, J=1.4, 8.2 Hz), 8.53 (1H, d, J=8.2 Hz).

35 (2) Tert-butyl [6-cyano-4-(4-methylphenyl)-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.27 g, 0.6

mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the 5 precipitated crystals were recrystallized from methanol - diethyl ether to give 3-(aminomethyl)-2-isobutyl-4-(4-methylphenyl)-1(2H)-isoquinolinone-6-carbonitrile hydrochloride (0.22 g, 95.7%) as crystals.

Melting point 278-279°C.

10 $^1\text{H-NMR}(\text{DMSO-d}_6)$ δ : 0.92 (6H, d, $J=6.6$ Hz), 1.99-2.16 (1H, m), 2.45 (3H, s), 3.90 (2H, s), 4.11 (2H, d, $J=7.0$ Hz), 7.25 (1H, d, $J=1.4$ Hz), 7.31 (2H, d, $J=7.9$ Hz), 7.41 (2H, d, $J=7.9$ Hz), 7.96 (1H, dd, $J=1.4$, 8.4 Hz), 8.47 (1H, d, $J=8.4$ Hz), 8.65 (3H, bs).

15 **Example 184**

(E)-3-[3-(Aminomethyl)-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenamide hydrochloride

(1) A suspension of tert-butyl [2-isobutyl-4-(4-methylphenyl)-1-oxo-6-trifluoromethanesulfonyloxy-1,2-dihydro-3-isoquinolinyl]methylcarbamate (Example 182 (1)) (1.42 g, 2.5 mmol), butyl acrylate (0.54 ml, 3.8 mmol), sodium hydrogencarbonate (0.32 g, 3.8 mmol), tetrabutylammonium chloride (83 mg, 0.3 mmol) and 25 palladium acetate (67 mg, 0.3 mmol) in N,N-dimethylformamide (30 ml) was stirred with heating at 100°C under an argon atmosphere for 20 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the 30 extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give butyl (E)-3-[3-[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-6-35 isoquinolinyl]-2-propenate (0.56 g, 40.3%) as an amorphous.

¹H-NMR(CDCl₃) δ: 0.95 (3H, t, J=7.8 Hz), 1.00 (6H, d, J=6.6 Hz), 1.35-1.47 (11H, m), 1.62-1.71 (2H, m), 2.18-2.29 (1H, m), 2.49 (3H, s), 4.08 (2H, d, J=6.0 Hz), 4.18 (2H, t, J=6.6 Hz), 4.22 (2H, d, J=4.8 Hz), 4.52 (1H, bs), 6.38 (1H, d, J=15.9 Hz), 7.04 (1H, d, J=1.0 Hz), 7.13 (2H, d, J=8.1 Hz), 7.33 (2H, d, J=8.1 Hz), 7.55 (1H, d, J=15.9 Hz), 7.61 (1H, dd, J=1.0, 8.4 Hz), 8.44 (1H, d, J=8.4 Hz).

- (2) To a solution of butyl ((E)-3-[3-[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenate (0.50 g, 0.9 mmol) in tetrahydrofuran (10 ml)-methanol (10 ml) was added 1N sodium hydroxide (2 ml). The obtained mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give (E)-3-[3-[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenic acid (0.38 g, 84.4%) as crystals.

Melting point 171-173°C.

Elemental analysis for C₂₉H₃₄N₂O₅ 0.25H₂O

Calculated: C, 70.35; H, 7.02; N, 5.66.

Found: C, 70.16; H, 6.94; N, 5.49.

¹H-NMR(CDCl₃) δ: 0.99 (6H, d, J=6.6 Hz), 1.48 (9H, s),

- 2.08-2.29 (1H, m), 2.50 (3H, s), 4.05 (2H, d, J=6.3 Hz), 4.17 (2H, d, J=4.5 Hz), 5.46 (1H, bs), 6.30 (1H, d, J=15.9 Hz), 6.88 (1H, s), 7.20 (2H, d, J=7.6 Hz), 7.34 (2H, d, J=7.6 Hz), 7.41 (1H, d, J=8.6 Hz), 7.47 (1H, d, J=15.9 Hz), 8.29 (1H, d, J=8.6 Hz).

- (3) A solution of (E)-3-[3-[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-4-(4-

methylphenyl)-1-oxo-1,2-dihydro-6-isooquinolinyl]-2-propenic acid (0.25 g, 0.5 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.19 g, 1 mmol) and 1-hydroxybenzotriazole ammonium salt (0.15 g, 1 mmol) in N,N-dimethylformamide (10 ml) was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give (E)-3-[3-[(tert-butoxycarbonyl)-amino]methyl]-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-6-isooquinolinyl]-2-propenamide (0.21 g, 84.0%) as crystals.

Melting point 152-154°C.

Elemental analysis for $C_{29}H_{35}N_3O_4 \cdot 0.75H_2O$

Calculated: C, 69.23; H, 7.31; N, 8.35.

Found: C, 69.58; H, 7.29; N, 8.01.

1H -NMR($CDCl_3$) δ : 1.00 (6H, d, $J=6.6$ Hz), 1.43 (9H, s), 2.16-2.28 (1H, m), 2.48 (3H, s), 4.07 (2H, d, $J=7.4$ Hz), 4.22 (2H, d, $J=5.6$ Hz), 4.70 (1H, bs), 5.71 (2H, bs), 6.40 (1H, d, $J=15.6$ Hz), 7.00 (1H, s), 7.12 (2H, d, $J=7.8$ Hz), 7.32 (2H, d, $J=7.8$ Hz), 7.44-7.54 (2H, m), 8.36 (1H, d, $J=8.4$ Hz).

(4) (E)-3-[3-[(Tert-butoxycarbonyl)amino]methyl]-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-6-isooquinolinyl]-2-propenamide (0.15 g, 0.3 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was crystallized from ethyl acetate - diisopropyl ether to give (E)-3-[3-(aminomethyl)-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-6-isooquinolinyl]-2-propenamide hydrochloride (0.12 g, 92.3%) as crystals.

Melting point 264-266°C.

Elemental analysis for $C_{24}H_{28}N_3O_2Cl$ 1.25H₂O

Calculated: C, 64.28; H, 6.85; N, 9.37.

Found: C, 64.37; H, 6.88; N, 9.08.

¹H-NMR(DMSO-d₆) δ: 0.92 (6H, d, J=6.6 Hz), 2.04-2.16 (1H, m), 3.87 (2H, d, J=2.4 Hz), 4.08 (2H, d, J=6.9 Hz), 6.56 (1H, d, J=15.9 Hz), 7.00 (1H, d, J=1.2 Hz), 7.18 (1H, bs), 7.25-7.42 (5H, m), 7.67 (1H, bs), 7.77 (1H, dd, J=1.2, 8.7 Hz), 8.34 (1H, d, J=8.7 Hz), 8.53 (3H, bs).

Example 185

- ¹⁰ 2-[[3-(Aminomethyl)-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]oxy]acetamide hydrochloride (1) A mixed solution of methyl 6-benzyloxy-2-isobutyl-1-oxo-4-trifluoromethanesulfonyloxy-1,2-dihydro-3-isoquinolinecarboxylate (10.27 g, 20 mmol), 4-¹⁵ chlorophenylboronic acid (3.75 g, 24 mmol) and sodium carbonate (5.30 g, 50 mmol) in toluene (50 ml)-methanol (10 ml)-water (10 ml) was stirred under an argon atmosphere at room temperature for 30 min. To the obtained mixture was added ²⁰ tetrakis(triphenylphosphine)palladium (1.15 g, 1 mmol) and the mixture was refluxed under heating under an argon atmosphere for 10 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was ²⁵ dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give methyl 6-benzyloxy-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (5.21 g, 54.8%) as ³⁰ crystals.

Melting point 165.5-166°C.

Elemental analysis for $C_{28}H_{26}NO_4Cl$

Calculated: C, 70.66; H, 5.51; N, 2.94.

Found: C, 70.89; H, 5.68; N, 2.78.

- ³⁵ ¹H-NMR(CDCl₃) δ: 0.91 (6H, d, J=7.0 Hz), 2.03-2.21 (1H, m), 3.50 (3H, s), 3.93 (2H, d, J=7.8 Hz), 4.99 (2H, s),

6.52 (1H, d, J=2.6 Hz), 7.15-7.22 (3H, m), 7.26-7.44 (7H, m), 8.42 (1H, d, J=8.8 Hz).

(2) To a suspension of methyl 6-benzyloxy-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-

⁵ isoquinolinecarboxylate (5.00 g, 10.5 mmol) in 1,4-dioxane (50 ml) was added an aqueous solution (20 ml) of lithium hydroxide monohydrate (1.32 g, 31.5 mmol). The obtained mixture was refluxed under heating for 24 h.

The reaction mixture was poured into water, acidified

¹⁰ with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from tetrahydrofuran - n-hexane to give

¹⁵ 6-benzyloxy-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (4.69 g, 96.7%) as crystals.

Melting point 200-201°C.

Elemental analysis for C₂₇H₂₄NO₄Cl

²⁰ Calculated: C, 70.20; H, 5.24; N, 3.03.

Found: C, 70.12; H, 5.28; N, 2.97.

¹H-NMR(CDCl₃) δ: 0.86 (6H, d, J=6.6 Hz), 2.07-2.25 (1H, m), 3.90 (2H, d, J=7.2 Hz), 5.00 (2H, s), 6.51 (1H, d, J=2.4 Hz), 7.14 (1H, dd, J=2.4, 9.0 Hz), 7.21-7.40 (9H, m), 8.25 (1H, d, J=9.0 Hz).

(3) To a mixture of 6-benzyloxy-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (4.62 g, 10 mmol) and tetrahydrofuran (50 ml) were added oxalyl chloride (1.0 ml, 15.6 mmol) and N,N-dimethylformamide (3 drops), and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in tetrahydrofuran (20 ml). The obtained solution was added dropwise to a suspension of sodium tetrahydronborate (1.32 g, 35 mmol) in 1,2-dimethoxyethane (30 ml) at 0°C. The obtained mixture was

stirred at 0°C for 1 h. The reaction mixture was poured into 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under

5 reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give 6-benzyloxy-4-(4-chlorophenyl)-3-hydroxymethyl-2-isobutyl-1(2H)-isoquinolinone (4.31 g, 96.4%) as crystals.

10 Melting point 87-88°C.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ : 0.95 (6H, d, $J=6.6$ Hz), 2.11-2.28 (1H, m), 2.39 (1H, bs), 4.16 (2H, d, $J=7.6$ Hz), 4.41 (2H, d, $J=5.4$ Hz), 4.92 (2H, s), 6.29 (1H, d, $J=2.4$ Hz), 7.00 (1H, dd, $J=2.4$, 9.0 Hz), 7.21-7.38 (7H, m), 7.45 (2H, d, $J=8.4$ Hz), 8.27 (1H, d, $J=8.8$ Hz).

15 (4) To a suspension of 6-benzyloxy-4-(4-chlorophenyl)-3-hydroxymethyl-2-isobutyl-1(2H)-isoquinolinone (4.25 g, 9.5 mmol) in toluene (50 ml) was added thionyl chloride (1.4 ml; 19 mmol). The obtained mixture was refluxed
20 under heating for 2 h. The reaction mixture was poured into saturated aqueous sodium hydrogen carbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give

25 6-benzyloxy-3-chloromethyl-4-(4-chlorophenyl)-2-isobutyl-1(2H)-isoquinolinone (3.98 g, 89.8%) as an oil.
 $^1\text{H-NMR}(\text{CDCl}_3)$ δ : 0.99 (6H, d, $J=7.0$ Hz), 2.13-2.30 (1H, m), 4.14 (2H, d, $J=7.6$ Hz), 4.34 (2H, s), 4.96 (2H, s), 6.34 (1H, d, $J=2.2$ Hz), 7.06-7.38 (8H, m), 7.44-7.50 (2H, m), 8.41 (1H, d, $J=8.8$ Hz).

30 (5) A solution of 6-benzyloxy-3-chloromethyl-4-(4-chlorophenyl)-2-isobutyl-1(2H)-isoquinolinone (3.96 g, 8.5 mmol) and potassium phthalimide (2.37 g, 12.8 mmol) in N,N-dimethylformamide (40 ml) was stirred at room
35 temperature for 6 h. The reaction mixture was poured into water and extracted with ethyl acetate. After

washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 2-[(6-benzyloxy-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl]-1H-isoindole-1,3(2H)-dione (4.72 g, 96.3%) as crystals.

Melting point 182-183°C.

Elemental analysis for C₃₅H₂₉N₂O₄Cl

Calculated: C, 72.85; H, 5.07; N, 4.85.

Found: C, 72.95; H, 5.19; N, 4.70.

¹H-NMR(CDCl₃) δ: 0.98 (6H, d, J=6.6 Hz), 2.09-2.31 (1H, m), 4.00 (2H, d, J=7.2 Hz), 4.74 (2H, s), 4.93 (2H, s), 6.29 (1H, d, J=2.6 Hz), 7.11 (1H, dd, J=2.6, 8.8 Hz),

7.19-7.41 (9H, m), 7.66-7.79 (4H, m), 8.38 (1H, d, J=8.8 Hz).

(6) To a suspension of 2-[(6-benzyloxy-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl]-1H-isoindole-1,3(2H)-dione (4.61 g,

8 mmol) in ethanol (50 ml) was added hydrazine monohydrate (1.2 ml, 24 mmol). The obtained mixture was refluxed under heating for 1 h. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate.

The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (50 ml) and di-t-butyl dicarbonate (2.8 ml, 12 mmol) was added thereto. The obtained mixture

was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were

recrystallized from ethyl acetate - diisopropyl ether to give tert-butyl [6-benzyloxy-4-(4-chlorophenyl)-2-

isobutyl-1-oxo-1,2-dihydro-3-
isoquinolinyl)methylcarbamate (4.16 g, 95.2%) as
crystals.

Melting point 186-187°C.

5 Elemental analysis for C₃₂H₃₅N₂O₄Cl

Calculated: C, 70.25; H, 6.45; N, 5.12.

Found: C, 70.17; H, 6.43; N, 5.00.

¹H-NMR(CDCl₃) δ: 0.98 (6H, d, J=6.6 Hz), 1.42 (9H, s),
2.14-2.28 (1H, m), 4.02 (2H, d, J=7.6 Hz), 4.15 (2H, d,
J=5.2 Hz), 4.46 (1H, bs), 4.95 (2H, s), 6.28 (1H, d,
J=2.6 Hz), 7.07-7.16 (3H, m), 7.22-7.37 (5H, m), 7.42-
7.49 (2H, m), 8.37 (1H, d, J=8.8 Hz).

(7) Tert-butyl [6-benzyloxy-4-(4-chlorophenyl)-2-
isobutyl-1-oxo-1,2-dihydro-3-

15 isoquinolinyl)methylcarbamate (0.54 g, 1 mmol) was
suspended in 48% aqueous solution (20 ml) of hydrogen
bromide and the obtained mixture was refluxed under
heating for 3 h. The reaction mixture was neutralized
with 1N sodium hydroxide aqueous solution and extracted

20 with ethyl acetate. The extract was washed with brine,
dried over anhydrous magnesium sulfate and concentrated
under reduced pressure. The residue was dissolved in
tetrahydrofuran (10 ml) and di-t-butyl dicarbonate (0.28
ml, 1 mmol) was added thereto. The obtained mixture was

25 stirred at room temperature for 1 h. The reaction
mixture was poured into water and extracted with ethyl
acetate. The extract was washed with brine, dried over
anhydrous magnesium sulfate and concentrated under
reduced pressure. The residue was purified by silica

30 gel column chromatography to give tert-butyl [4-(4-
chlorophenyl)-6-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-
isoquinolinyl)methylcarbamate (0.32 g, 71.1%) as
crystals.

Melting point 220-221°C.

35 ¹H-NMR(CDCl₃) δ: 0.95 (6H, d, J=6.6 Hz), 1.42 (9H, s),
2.08-2.29 (1H, m), 4.01 (2H, d, J=7.0 Hz), 4.13 (2H, d,

J=5.6 Hz), 4.50 (1H, bs), 6.33 (1H, d, J=2.4 Hz), 7.03 (1H, dd, J=2.4, 8.8 Hz), 7.03 (2H, d, J=8.2 Hz), 7.40 (2H, d, J=8.2 Hz), 7.93 (1H, bs), 8.26 (1H, d, J=8.8 Hz).

(8) To a solution of tert-butyl [4-(4-chlorophenyl)-6-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.45 g, 1 mmol) in N,N-dimethylformamide (10 ml) was added sodium hydride (48 mg, 1.2 mmol) (60% in oil) at 0°C, and the mixture was stirred at 0°C for 10 min. To the obtained mixture was added 2-iodoacetamide (0.22 g, 1.2 mmol) and the mixture was stirred at 0°C for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [6-(2-amino-2-oxoethoxy)-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.27 g, 52.9%) as crystals.

(20) Melting point 241-242°C.

Elemental analysis for C₂₇H₃₂N₃O₅Cl

Calculated: C, 63.09; H, 6.27; N, 8.17.

Found: C, 63.07; H, 6.32; N, 8.22.

¹H-NMR(CDCl₃) δ: 0.99 (6H, d, J=6.6 Hz), 1.43 (9H, s), 2.10-2.28 (1H, m), 4.04 (2H, d, J=7.4 Hz), 4.17 (2H, d, J=5.4 Hz), 4.35 (2H, s), 4.56 (1H, bs), 5.79 (1H, bs), 6.28 (1H, d, J=2.4 Hz), 6.50 (1H, bs), 7.04 (1H, dd, J=2.4, 9.0 Hz), 7.17-7.24 (2H, m), 7.47-7.53 (2H, m), 8.41 (1H, d, J=9.0 Hz).

(9) Tert-butyl [6-(2-amino-2-oxoethoxy)-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.20 g, 0.4 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the

precipitated crystals were recrystallized from ethyl acetate - diisopropyl ether to give 2-[[3-(aminomethyl)-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]oxy]acetamide hydrochloride (0.16 g,

⁵ 88.9%) as crystals.

Melting point 260-262°C.

¹H-NMR(DMSO-d₆) δ: 0.91 (6H, d, J=6.6 Hz), 1.99-2.18 (1H, m), 3.84 (2H, bs), 4.03 (2H, d, J=7.4 Hz), 4.39 (2H, s), 6.31 (1H, d, J=2.4 Hz), 7.21 (1H, dd, J=2.4, 9.0 Hz),
¹⁰ 7.36 (1H, bs), 7.40 (2H, d, J=8.4 Hz), 7.59 (1H, bs), 7.62 (2H, d, J=8.4 Hz), 8.27 (1H, d, J=9.0 Hz), 8.51 (3H, s).

Example 186

3-(Aminomethyl)-4-(4-chlorophenyl)-2-isobutyl-1(2H)-

¹⁵ isoquinolinone-6-carboxamide hydrochloride

(1) To a solution of tert-butyl [6-hydroxy-4-(4-

chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-

isoquinolinyl]methylcarbamate (Example 185(7)) (1.83 g, 4 mmol) in N,N-dimethylformamide (20 ml) was added

²⁰ sodium hydride (0.24 g, 6 mmol) (60% in oil) at 0°C, and the mixture was stirred at 0°C for 10 min. To the obtained mixture was added N-

phenyltrifluoromethanesulfonimide (2.14 g, 6 mmol) and the mixture was stirred at room temperature for 2 h.

²⁵ The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography

³⁰ to give tert-butyl [4-(4-chlorophenyl)-2-isobutyl-1-oxo-6-trifluoromethanesulfonyloxy-1,2-dihydro-3-isoquinolinyl]methylcarbamate (2.36 g, 100%) as an oil.

¹H-NMR(CDCl₃) δ: 0.98 (6H, d, J=7.0 Hz), 1.43 (9H, s), 2.04-2.26 (1H, m), 4.07 (2H, d, J=7.4 Hz), 4.21 (2H, d,
³⁵ J=5.4 Hz), 4.50 (1H, bs), 6.81 (1H, d, J=2.6 Hz), 7.17-7.26 (2H, m), 7.50-7.57 (3H, m), 8.54 (1H, d, J=8.8 Hz).

(2) A mixed solution of tert-butyl [4-(4-chlorophenyl)-2-isobutyl-1-oxo-6-trifluoromethanesulfonyloxy-1,2-dihydro-3-isoquinolinyl]methylcarbamate (2.35 g, 4 mmol), 1,1'-bis(diphenylphosphino)ferrocene (0.11 g, 0.2 mmol), triethylamine (0.6 ml, 4.4 mmol) and palladium acetate (45 mg, 0.2 mmol) in tetrahydrofuran (20 ml)-methanol (20 ml) was stirred with heating at 100°C under a carbon monoxide atmosphere at 5 atm for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give methyl 3-[(tert-butoxycarbonyl)amino]methyl]-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylate (1.71 g, 85.9%) as crystals. Melting point 205-207°C.

Elemental analysis for C₂₇H₃₁N₂O₅Cl

Calculated: C, 64.99; H, 6.26; N, 5.61.

Found: C, 64.91; H, 6.44; N, 5.34.

¹H-NMR(CDCl₃) δ: 1.00 (6H, d, J=6.6 Hz), 1.44 (9H, s), 2.14-2.30 (1H, m), 3.87 (3H, s), 4.08 (2H, d, J=7.2 Hz), 4.20 (2H, d, J=5.6 Hz), 4.55 (1H, bs), 7.19-7.25 (2H, m), 7.49-7.56 (2H, m), 7.61 (1H, d, J=1.5 Hz), 8.03 (1H, dd, J=1.5, 8.5 Hz), 8.49 (1H, d, J=8.5 Hz).

(3) To a solution of methyl 3-[(tert-butoxycarbonyl)amino]methyl]-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylate (1.50 g, 3 mmol) in tetrahydrofuran (10 ml)-methanol (10 ml) was added 1N sodium hydroxide (6 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized

from tetrahydrofuran - isopropyl ether to give 3-[(*tert*-butoxycarbonyl)amino]methyl]-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid (1.41 g, 97.2%) as crystals.

⁵ Melting point 226-227°C.

Elemental analysis for C₂₆H₂₉N₂O₅Cl

Calculated: C, 64.39; H, 6.03; N, 5.78.

Found: C, 64.50; H, 6.36; N, 5.37.

¹H-NMR(CDCl₃) δ: 0.98 (6H, d, J=6.6 Hz), 1.49 (9H, s),

¹⁰ 2.10-2.26 (1H, m), 4.04 (2H, d, J=6.6 Hz), 4.14 (2H, s), 5.65 (1H, bs), 7.29 (2H, d, J=8.2 Hz), 7.44 (1H, s), 7.52 (2H, d, J=8.2 Hz), 7.83 (1H, d, J=8.0 Hz), 8.32 (1H, d, J=8.0 Hz).

(4) A solution of 3-[(*tert*-

¹⁵ butoxycarbonyl)amino]methyl]-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid (1.21 g, 2.5 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.96 g, 5 mmol) and 1-hydroxybenzotriazole ammonium salt (0.76 g,

²⁰ 5 mmol) in N,N-dimethylformamide (10 ml) was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced

²⁵ pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give 3-[(*tert*-butoxycarbonyl)amino]methyl]-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxamide (1.02 g, 85.0%) as crystals.

³⁰ Melting point 144-146°C.

Elemental analysis for C₂₆H₃₀N₂O₄Cl 0.25H₂O

Calculated: C, 63.93; H, 6.29; N, 8.60.

Found: C, 64.06; H, 6.06; N, 8.53.

¹H-NMR(CDCl₃) δ: 0.99 (6H, d, J=6.6 Hz), 1.45 (9H, s),

³⁵ 2.14-2.26 (1H, m), 4.06 (2H, d, J=6.9 Hz), 4.18 (2H, d, J=4.5 Hz), 4.92 (1H, bs), 5.89 (1H, bs), 6.22 (1H, bs),

7.24 (2H, d, J=8.4 Hz), 7.35 (1H, d, J=1.2 Hz), 7.50 (2H, d, J=8.4 Hz), 7.66 (1H, dd, J=1.2, 8.4 Hz), 8.35 (1H, d, J=8.4 Hz).

(5) 3-[[(Tert-butoxycarbonyl)amino]methyl]-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxamide (0.48 g, 1 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the precipitated crystals were recrystallized from methanol-diethyl ether to give 3-(aminomethyl)-4-(4-chlorophenyl)-2-isobutyl-1(2H)-isoquinolinone-6-carboxamide hydrochloride (0.41 g, 97.6%) as crystals.

15 Melting point 260-261°C.

¹H-NMR(DMSO-d₆) δ: 0.92 (6H, d, J=6.6 Hz), 1.99-2.17 (1H, m), 3.85 (2H, s), 4.08 (2H, d, J=7.0 Hz), 7.44 (2H, d, J=8.0 Hz), 7.45 (1H, d, J=1.5 Hz), 7.60 (1H, bs), 7.64 (2H, d, J=8.0 Hz), 8.01 (1H, d, J=1.5, 8.4 Hz), 8.19 (1H, bs), 8.38 (1H, d, J=8.4 Hz), 8.56 (3H, bs).

Example 187

3-(Aminomethyl)-4-(4-chlorophenyl)-2-isobutyl-1(2H)-isoquinolinone-6-carbonitrile hydrochloride.

(1) A solution of 3-[[(tert-butoxycarbonyl)amino]methyl]-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxamide (Example 186 (4)) (0.48 g, 1 mmol) and cyanuric chloride (0.55 g, 3 mmol) in N,N-dimethylformamide (10 mmol) was stirred at 0°C for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [4-(4-chlorophenyl)-6-cyano-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.37 g, 80.4%) as crystals.

Melting point 234-235°C.

Elemental analysis C₂₆H₂₈N₃O₃Cl

Calculated: C, 67.02; H, 6.06; N, 9.02.

Found: C, 67.10; H, 6.09; N, 9.07.

⁵ ¹H-NMR(CDCl₃) δ: 1.00 (6H, d, J=6.6 Hz), 1.43 (9H, s), 2.16-2.30 (1H, m), 4.08 (2H, d, J=7.4 Hz), 4.22 (2H, d, J=5.8 Hz), 4.44 (1H, bs), 7.16-7.23 (2H, m), 7.26 (1H, d, J=1.6 Hz), 7.51-7.58 (2H, m), 7.65 (1H, dd, J=1.6, 8.6 Hz), 8.55 (1H, d, J=8.6 Hz).

¹⁰ (2) Tert-butyl [4-(4-chlorophenyl)-6-cyano-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.28 g, 0.6 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room temperature for 1 h. The reaction.

¹⁵ mixture was concentrated under reduced pressure, and the precipitated crystals were recrystallized from methanol - diethyl ether to give 3-(aminomethyl)-4-(4-chlorophenyl)-2-isobutyl-1(2H)-isoquinolinone-6-carbonitrile hydrochloride (0.23 g, 95.8%) as crystals.

²⁰ Melting point 280-281°C.

Elemental analysis for C₂₁H₂₁N₃OCl

Calculated: C, 62.69; H, 5.26; N, 10.44.

Found: C, 62.34; H, 5.31; N, 10.45.

¹H-NMR(DMSO-d₆) δ: 0.93 (6H, d, J=6.6 Hz), 1.99-2.19 (1H, m), 3.87 (2H, s), 4.10 (2H, d, J=7.4 Hz), 7.32 (1H, d, J=1.4 Hz), 7.43-7.49 (2H, m), 7.64-7.68 (2H, m), 7.97 (1H, dd, J=1.4, 8.4 Hz), 8.47 (1H, d, J=8.4 Hz), 8.67 (3H, bs).

Example 188

³⁰ (E)-3-[3-(Aminomethyl)-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenamide hydrochloride

(1) A suspension of tert-butyl [4-(4-chlorophenyl)-2-isobutyl-1-oxo-6-trifluoromethanesulfonyloxy-1,2-

³⁵ dihydro-3-isoquinolinyl]methylcarbamate (Example 186 (1)) (2.06 g, 3.5 mmol), butyl acrylate (0.76 ml, 5.3

mmol), sodium hydrogencarbonate (0.45 g, 5.3 mmol), tetrabutylammonium chloride (0.11 g, 0.4 mmol) and palladium acetate (0.09 g, 0.4 mmol) in N,N-dimethylformamide (20 ml) was stirred with heating at 5 100°C under an argon atmosphere for 48 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was 10 purified by silica gel column chromatography to give butyl (E)-3-[3-[(tert-butoxycarbonyl)amino]methyl]-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenate (0.48 g, 23.8%) as crystals. Melting point 149-150°C.

15 Elemental analysis for $C_{32}H_{39}N_2O_5Cl$ 0.25H₂O
Calculated: C, 67.24; H, 6.97; N, 4.90.
Found: C, 67.22; H, 7.01; N, 4.93.
¹H-NMR(CDCl₃) δ: 0.95 (3H, t, J=7.4 Hz), 1.00 (6H, d, J=6.4 Hz), 1.32-1.50 (11H, m), 1.59-1.71 (2H, m), 2.14-2.30 (1H, m), 4.07 (2H, d, J=7.6 Hz), 4.16-4.22 (4H, m), 4.43 (1H, bs), 6.40 (1H, d, J=16.2 Hz), 6.98 (1H, d, J=1.4 Hz), 7.20 (2H, d, J=8.4 Hz), 7.52 (2H, d, J=8.4 Hz), 7.55 (1H, d, J=16.2 Hz), 7.63 (1H, dd, J=1.4, 8.4 Hz), 8.45 (1H, d, J=8.4 Hz).

20 25 (2) To a solution of butyl (E)-3-[3-[(tert-butoxycarbonyl)amino]methyl]-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenate (0.41 g, 0.7 mmol) in tetrahydrofuran (10 ml)-methanol (10 ml) was added 1N sodium hydroxide (2 ml) and the 30 mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced 35 pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give (E)-3-[3-

[(tert-butoxycarbonyl)amino]methyl]-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenic acid (0.34 g, 91.9%) as crystals.

Melting point 147-149°C.

- 5 Elemental analysis for $C_{28}H_{31}N_2O_5Cl$ 0.25H₂O
 Calculated: C, 65.24; H, 6.16; N, 5.43.
 Found: C, 65.18; H, 6.15; N, 5.31.
¹H-NMR(CDCl₃) δ: 0.99 (6H, d, J=6.4 Hz), 1.48 (9H, s), 2.08-2.28 (1H, m), 4.05 (2H, d, J=5.8 Hz), 4.14 (2H, s), 5.46 (1H, bs), 6.32 (1H, d, J=15.8 Hz), 6.82 (1H, s), 7.26-7.31 (2H, m), 7.42-7.56 (4H, m), 8.28 (1H, d, J=7.8 Hz).
- (3) A solution of (E)-3-[3-[(tert-butoxycarbonyl)amino]methyl]-4-(4-chlorophenyl)-2-
 15 isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenic acid (0.20 g, 0.4 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.15 g, 0.8 mmol) and 1-hydroxybenzotriazole ammonium salt (0.12 g, 0.8 mmol) in N,N-dimethylformamide (10 ml) was
 20 stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was crystallized from
 25 ethyl acetate - n-hexane to give (E)-3-[3-[(tert-butoxycarbonyl)amino]methyl]-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenamide (0.18 g, 90.0%) as crystals.
- Melting point 152-154°C.
- 30 Elemental analysis for $C_{28}H_{31}N_3O_4Cl$ 0.25H₂O
 Calculated: C, 65.36; H, 6.37; N, 8.17.
 Found: C, 65.30; H, 6.27; N, 7.99.
¹H-NMR(CDCl₃) δ: 0.99 (6H, d, J=6.6 Hz), 1.45 (9H, s), 2.12-2.28 (1H, m), 4.05 (2H, d, J=7.2 Hz), 4.18 (2H, d, J=4.6 Hz), 4.95 (1H, bs), 5.72 (1H, bs), 5.85 (1H, bs), 6.37 (1H, d, J=15.8 Hz), 6.91 (1H, d, J=1.2 Hz), 7.24

(2H, d, J=8.8 Hz), 7.41-7.54 (4H, m), 8.28 (1H, d, J=8.4 Hz).

(4) A solution of (E)-3-[3-[(tert-butoxycarbonyl)amino]methyl]-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenamide (0.15 g, 0.3 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was crystallized from ethyl acetate to give (E)-3-[3-(aminomethyl)-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenamide hydrochloride (0.12 g, 92.3%) as crystals.

15 Melting point 261-263°C.

Elemental analysis for $C_{23}H_{25}N_3O_2Cl_2 \cdot 0.75H_2O$

Calculated: C, 60.07; H, 5.81; N, 9.14.

Found: C, 59.78; H, 6.14; N, 8.75.

1H -NMR(DMSO-d₆) δ: 0.92 (6H, d, J=6.6 Hz), 1.91-2.21 (1H, m), 3.85 (2H, s), 4.06 (2H, d, J=7.4 Hz), 6.58 (1H, d, J=15.8 Hz), 7.02 (1H, s), 7.19 (1H, bs), 7.34-7.47 (3H, m), 7.62-7.67 (3H, m), 7.79 (1H, d, J=8.0 Hz), 8.35 (1H, d, J=8.0 Hz), 8.60 (3H, bs).

Example 189

25 3-(Aminomethyl)-4-butoxy-2-isobutyl-6-(4-methyl-1,3-thiazol-2-yl)-1(2H)-isoquinolinone dihydrochloride
(1) To a suspension of 3-[(tert-butoxycarbonyl)amino]methyl]-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxamide (0.44 g, 1 mmol)
30 in toluene (20 ml) was added Lawesson's reagent (0.24 g, 0.6 mmol), and the mixture was refluxed under heating for 1 h. The reaction mixture was purified by silica gel column chromatography to give tert-butyl [6-(aminothiocarbonyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.18 g, 39.1%) as crystals.

Melting point 189-190°C.

Elemental analysis for C₂₄H₃₅N₃O₄S

Calculated: C, 62.44; H, 7.64; N, 9.10.

Found: C, 62.38; H, 7.51; N, 8.89.

5 ¹H-NMR(CDCl₃) δ: 0.93 (6H, d, J=6.6 Hz), 1.02 (3H, t, J=7.3 Hz), 1.50-1.64 (11H, m), 1.80-1.93 (2H, m), 2.04-2.18 (1H, m), 3.83 (2H, t, J=6.8 Hz), 3.96 (2H, d, J=7.4 Hz), 4.48 (2H, d, J=5.6 Hz), 5.37 (1H, bs), 7.67 (1H, d, J=8.3 Hz), 7.83-7.90 (2H, m), 8.05 (1H, d, J=8.3 Hz),
10 8.31 (1H, bs).

(2) A suspension of tert-butyl [6-(aminothiocarbonyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]-methylcarbamate (0.46 g, 1 mmol), bromoacetone (0.20 g, 1.5 mmol) and sodium acetate (0.12 g, 1.5 mmol) in

15 ethanol (10 ml) was refluxed under heating for 12 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by
20 silica gel column chromatography to give tert-butyl[4-butoxy-2-isobutyl-6-(4-methyl-1,3-thiazol-2-yl)-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.36 g, 73.5%) as an amorphous.

Elemental analysis for C₂₇H₃₇N₃O₄S

25 Calculated: C, 64.90; H, 7.46; N, 8.41.

Found: C, 64.63; H, 7.58; N, 8.26.

¹H-NMR(CDCl₃) δ: 0.98 (6H, d, J=7.0 Hz), 1.07 (3H, t, J=7.3 Hz), 1.47 (9H, s), 1.56-1.75 (2H, m), 1.84-1.98 (2H, m), 2.12-2.26 (1H, m), 2.55 (3H, d, J=0.8 Hz), 3.92

30 (2H, t, J=6.4 Hz), 4.00 (2H, d, J=7.4 Hz), 4.54 (2H, d, J=5.8 Hz), 4.78 (1H, bs), 6.98 (1H, q, J=0.8 Hz), 8.08 (1H, dd, J=1.8, 8.4 Hz), 8.22 (1H, d, J=1.8 Hz), 8.46 (1H, d, J=8.4 Hz).

(3) Tert-butyl [4-butoxy-2-isobutyl-6-(4-methyl-1,3-thiazol-2-yl)-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.30 g, 0.6 mmol) was

dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the precipitated crystals were recrystallized from methanol - diisopropyl ether to give 3-(aminomethyl)-4-butoxy-2-isobutyl-6-(4-methyl-1,3-thiazol-2-yl)-1(2H)-isoquinolinone dihydrochloride (0.27 g, 96.4%) as crystals.

Melting point 201-202°C.

¹H-NMR(DMSO-d₆) δ: 0.90 (6H, d, J=6.6 Hz), 1.04 (3H, t, J=7.1 Hz), 1.56-1.74 (2H, m), 1.82-2.12 (3H, m), 2.48 (3H, d, J=0.6 Hz), 3.98-4.02 (4H, m), 4.21 (2H, d, J=5.2 Hz), 7.51 (1H, q, J=0.6 Hz), 8.13 (1H, dd, J=1.6, 8.4 Hz), 8.25 (1H, d, J=1.6 Hz), 8.37 (1H, d, J=8.4 Hz), 8.76 (3H, bs).

Example 190

Ethyl 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylate hydrochloride

(1) Tert-butyl [6-(aminothiocarbonyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (Example 189 (1)) (1.38 g, 3 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (10 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was suspended in tetrahydrofuran (20 ml). To the obtained mixture were added triethylamine (0.84 ml, 6 mmol) and 9-fluorenylmethylchloroformate (1.16 g, 4.5 mmol) and the mixture was stirred at 0°C for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 9H-fluoren-9-

ylmethyl [6-(aminocarbothioyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (1.52 g, 86.9%) as an amorphous.

¹H-NMR(CDCl₃) δ: 0.94-1.00 (9H, m), 1.47-1.59 (2H, m),

⁵ 1.74-1.83 (2H, m), 2.07-2.18 (1H, m), 3.77 (2H, t, J=6.3 Hz), 3.98 (2H, d, J=6.6 Hz), 4.25 (1H, t, J=6.6 Hz), 4.51-4.53 (4H, m), 5.79 (1H, bs), 7.26-7.41 (4H, m), 7.63-7.66 (3H, m), 7.75 (2H, d, J=7.2 Hz), 7.86 (1H, bs), 7.93 (1H, s), 8.00 (1H, bs), 8.12 (1H, d, J=8.1 Hz).

¹⁰ (2) A solution of 9H-fluoren-9-ylmethyl [6-(aminocarbothioyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.29 g, 0.5 mmol) and ethyl bromopyruvate (0.19 g, 1 mmol) in ethanol (10 ml) was refluxed under heating for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was crystallized from ethyl acetate - diisopropyl ether to give ethyl 2-[4-butoxy-3-[[[(9H-fluoren-9-ylmethoxy)carbonyl]amino)methyl]-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylate (0.30 g, 90.9%) as crystals.

Melting point 203-203.5°C.

²⁵ Elemental analysis for C₃₉H₄₁N₃O₆S

Calculated: C, 68.90; H, 6.08; N, 6.18.

Found: C, 68.64; H, 6.10; N, 6.06.

¹H-NMR(CDCl₃) δ: 0.97 (6H, d, J=6.6 Hz), 1.07 (3H, t, J=7.1 Hz), 1.45 (3H, t, J=7.0 Hz), 1.56-1.75 (2H, m),

³⁰ 1.81-1.98 (2H, m), 2.06-2.24 (1H, m), 3.94 (2H, t, J=6.4 Hz), 4.05 (2H, d, J=7.0 Hz), 4.22 (1H, t, J=6.6 Hz), 4.47 (2H, q, J=7.0 Hz), 4.49 (2H, d, J=6.6 Hz), 4.59 (2H, d, J=5.4 Hz), 5.23 (1H, bs), 7.29-7.43 (4H, m), 7.59 (2H, d, J=7.3 Hz), 8.14 (1H, dd, J=1.6, 8.4 Hz), 8.24-8.26 (2H, m), 8.47 (1H, d, J=8.4 Hz).

³⁵ (3) To a solution of ethyl 2-[4-butoxy-3-[[[(9H-fluoren-

9-ylmethoxy)carbonylamino]methyl]-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylate (1.70 g, 2.5 mmol) in N,N-dimethylformamide (25 ml)-tetrahydrofuran(25 ml) was added pyrrolidine (2 ml), and
5 the mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in
10 tetrahydrofuran (20 ml) and di-t-butyl dicarbonate (0.89 ml, 4 mmol) was added thereto. The obtained mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over
15 anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give ethyl 2-[4-butoxy-3-[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylate
20 (1.21 g, 87.1%) as crystals.

Melting point 172-172.5°C.

Elemental analysis: for C₂₉H₃₉N₃O₆S

Calculated: C, 62.45; H, 7.05; N, 7.53.

Found: C, 62.50; H, 7.04; N, 7.53.

25 ¹H-NMR(CDCl₃) δ: 0.98 (6H, d, J=6.6 Hz), 1.07 (3H, t, J=7.3 Hz), 1.45 (3H, t, J=7.2 Hz), 1.47 (9H, s), 1.62-1.78 (2H, m), 1.85-1.99 (2H, m), 2.12-2.26 (1H, m), 3.93 (2H, t, J=6.4 Hz), 4.01 (2H, d, J=7.2 Hz), 4.47 (2H, q, J=7.2 Hz), 4.54 (2H, d, J=6.6 Hz), 4.77 (1H, bs), 8.16 (1H, dd, J=1.8, 8.4 Hz), 8.25 (1H, s), 8.28 (1H, d, J=1.8 Hz), 8.49 (1H, d, J=8.4 Hz).

(4) Ethyl 2-[4-butoxy-3-[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylate

35 (0.17 g, 0.3 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml), and the

mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the precipitated crystals were recrystallized from ethyl acetate - diisopropyl ether to give ethyl 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylate hydrochloride (0.13 g, 92.9%) as crystals.

Melting point 224-226°C.

Elemental analysis for C₂₄H₃₂N₃O₄ClS H₂O

Calculated: C, 56.29; H, 6.69; N, 8.21.

Found: C, 56.00; H, 6.43; N, 7.99.

¹H-NMR(DMSO-d₆) δ: 0.91 (6H, d, J=6.6 Hz), 1.05 (3H, t, J=7.1 Hz), 1.36 (3H, t, J=7.2 Hz), 1.57-1.76 (2H, m), 1.83-2.16 (3H, m), 3.98-4.06 (4H, m), 4.22 (2H, d, J=4.6 Hz), 4.37 (2H, q, J=7.2 Hz), 8.20 (1H, dd, J=1.4, 8.4 Hz), 8.31 (1H, d, J=1.4 Hz), 8.42 (1H, d, J=8.4 Hz), 8.66 (3H, bs), 8.73 (1H, s).

Example 191

2-[3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylic acid hydrochloride

(1) To a solution of ethyl 2-[4-butoxy-3-[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylate

(1.12 g, 2 mmol) in tetrahydrofuran (10 ml)- ethanol (5 ml) was added 1N sodium hydroxide (4 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The

extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give 2-[4-butoxy-3-[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylic acid (0.97 g, 92.4%) as crystals.

Melting point 195-196°C.

Elemental analysis for C₂₇H₃₅N₃O₆S

Calculated: C, 61.23; H, 6.66; N, 7.93.

Found: C, 61.10; H, 6.71; N, 7.65.

- ⁵ ¹H-NMR(CDCl₃) δ: 0.98 (6H, d, J=7.0 Hz), 1.08 (3H, t, J=7.4 Hz), 1.48 (9H, s), 1.57-1.76 (2H, m), 1.85-1.99 (2H, m), 2.13-2.26 (1H, m), 3.93 (2H, t, J=6.2 Hz), 4.02 (2H, d, J=7.2 Hz), 4.56 (2H, d, J=5.6 Hz), 4.92 (1H, bs), 8.11 (1H, dd, J=1.8, 8.4 Hz), 8.24 (1H, d, J=1.8 Hz),
¹⁰ 8.36 (1H, s), 8.49 (1H, d, J=8.4 Hz).
(2) 2-[4-Butoxy-3-[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylic acid (0.16 g, 0.3 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was crystallized from ethyl acetate to give 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-
- ¹⁵ isoquinolinyl]-1,3-thiazole-4-carboxylic acid hydrochloride (0.13 g, 92.9%) as crystals.

Melting point 244-246°C.

Elemental analysis for C₂₂H₂₈N₃O₄ClS 0.5H₂O

Calculated: C, 55.63; H, 6.15; N, 8.85.

- ²⁵ Found: C, 55.45; H, 6.49; N, 8.51.

¹H-NMR(DMSO-d₆) δ: 0.91 (6H, d, J=6.6 Hz), 1.04 (3H, t, J=7.2 Hz), 1.60-1.72 (2H, m), 1.84-1.93 (2H, m), 2.00-2.10 (1H, m), 3.99-4.02 (4H, m), 4.22 (2H, s), 8.21 (1H, dd, J=1.5, 8.4 Hz), 8.30 (1H, d, J=1.5 Hz), 8.42 (1H, d, J=8.4 Hz), 8.63 (3H, bs), 8.66 (1H, s).

Example 192

2-[3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxamide hydrochloride

- ³⁵ (1) A solution of 2-[4-butoxy-3-[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-1,2-

dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylic acid (0.79 g, 1.5 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.58 g, 3 mmol) and 1-hydroxybenzotriazole ammonium salt (0.46 g, 3 mmol) in N,N-dimethylformamide (10 ml) was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from tetrahydrofuran-diisopropyl ether to give tert-butyl [6-[4-(aminocarbonyl)-1,3-thiazol-2-yl]-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.74 g, 93.7%) as crystals.

Melting point 195-196°C.

Elemental analysis for C₂₇H₃₆N₄O₄S 0.5H₂O

Calculated: C, 60.31; H, 6.94; N, 10.42.

Found: C, 60.62; H, 7.08; N, 10.19.

²⁰ ¹H-NMR(CDCl₃) δ: 0.98 (6H, d, J=6.8 Hz), 1.07 (3H, t, J=7.2 Hz), 1.48 (9H, s), 1.57-1.98 (4H, m), 2.11-2.28 (1H, m), 3.92 (2H, t, J=6.2 Hz), 4.02 (2H, d, J=7.4 Hz), 4.55 (2H, d, J=5.4 Hz), 4.91 (1H, bs), 5.89 (1H, bs), 7.29 (1H, bs), 8.04-8.09 (1H, m), 8.24-8.25 (1H, m), 8.46-8.51 (2H, m).

(2) Tert-butyl [6-[4-(aminocarbonyl)-1,3-thiazol-2-yl]-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.32 g, 0.6 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was crystallized from ethyl acetate to give 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxamide hydrochloride (0.26 g, 92.6%) as crystals.

Melting point 274-276°C.

Elemental analysis for $C_{22}H_{29}N_4O_3ClS \cdot 0.5H_2O$

Calculated: C, 55.74; H, 6.38; N, 11.82.

Found: C, 56.13; H, 6.33; N, 11.86.

¹H-NMR(DMSO-d₆) δ: 0.91 (6H, d, J=6.6 Hz), 1.04 (3H, t, J=7.1 Hz), 1.56-1.75 (2H, m), 1.84-2.18 (3H, m), 3.99-4.05 (4H, m), 4.22 (2H, d, J=4.4 Hz), 8.28 (1H, d, J=1.6 Hz), 8.30 (1H, dd, J=1.6, 9.2 Hz), 8.41 (1H, d, J=9.2 Hz), 8.46 (1H, s), 8.71 (3H, bs).

Example 193

¹⁰ 2-[3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carbonitrile hydrochloride

(1) A solution of tert-butyl[6-[4-(aminocarbonyl)-1,3-thiazol-2-yl]-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.32 g, 0.6 mmol) and cyanuric chloride (0.33 g, 1.8 mmol) in N,N-dimethylformamide (10 mmol) was stirred at 0°C for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [4-butoxy-6-(4-cyano-1,3-thiazol-2-yl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.28 g, 93.3%) as crystals.

Melting point 160-161°C.

Elemental analysis for $C_{27}H_{34}N_4O_4S$

Calculated: C, 63.51; H, 6.71; N, 10.97.

Found: C, 63.47; H, 6.69; N, 10.99.

³⁰ ¹H-NMR(CDCl₃) δ: 0.98 (6H, d, J=6.9 Hz), 1.08 (3H, t, J=7.5 Hz), 1.48 (9H, s), 1.60-1.72 (2H, m), 1.87-1.97 (2H, m), 2.12-2.24 (1H, m), 3.92 (2H, t, J=6.4 Hz), 4.01 (2H, d, J=7.5 Hz), 4.55 (2H, d, J=5.4 Hz), 4.86 (1H, bs), 8.01 (1H, dd, J=1.8, 8.2 Hz), 8.08 (1H, s), 8.29 (1H, d, J=1.8 Hz), 8.49 (1H, d, J=8.2 Hz).

(2) Tert-butyl [4-butoxy-6-(4-cyano-1,3-thiazol-2-yl)-2-

isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.20 g, 0.4 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room

5 temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was crystallized from ethyl acetate to give 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carbonitrile hydrochloride
10 (0.17 g, 94.4%) as crystals.

Melting point 167-169°C.

Elemental analysis for $C_{22}H_{27}N_4O_2ClS\ H_2O$

Calculated: C, 56.82; H, 6.29; N, 12.05.

Found: C, 56.92; H, 6.29; N, 11.95.

15 1H -NMR(DMSO-d₆) δ : 0.91 (6H, d, J=6.6 Hz), 1.05 (3H, t, J=7.2 Hz), 1.56-1.74 (2H, m), 1.82-2.18 (3H, m), 3.98-4.05 (4H, m), 4.22 (2H, s), 8.20 (1H, d, J=8.4 Hz), 8.30 (1H, s), 8.42 (1H, d, J=8.4 Hz), 8.70 (3H, bs), 9.06 (1H, s).

20 **Example 194**

3-(Aminomethyl)-2-isobutyl-6-(4-methyl-1,3-thiazol-2-yl)-4-phenyl-1(2H)-isoquinolinone

(1) To a suspension of 3-[(tert-butoxycarbonyl)amino]methyl-2-isobutyl-4-phenyl-1-oxo-

25 1,2-dihydro-6-isoquinolinecarboxamide (4.05 g, 9 mmol) in toluene (50 ml) was added Lawesson's reagent (2.19 g, 5.4 mmol), and the mixture was refluxed under heating for 1 h. The reaction mixture was purified by silica gel column chromatography to give tert-butyl [6-

30 (aminothiocarbonyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (3.64 g, 86.9%) as crystals.

Melting point 228-229°C.

Elemental analysis for $C_{26}H_{31}N_3O_3S$

35 Calculated: C, 67.07; H, 6.71; N, 9.02.

Found: C, 66.88; H, 6.66; N, 8.85.

¹H-NMR(CDCl₃) δ: 0.98 (6H, d, J=6.6 Hz), 1.44 (9H, s), 2.12-2.29 (1H, m), 4.07 (2H, d, J=6.9 Hz), 4.20 (2H, d, J=5.1 Hz), 4.79 (1H, bs), 7.23-7.27 (2H, m), 7.33 (1H, d, J=1.6 Hz), 7.37 (1H, bs), 7.46-7.56 (3H, m), 7.74 (1H, bs), 7.76 (1H, dd, J=1.6, 8.6 Hz), 8.29 (1H, d, J=8.6 Hz).

(2) Tert-butyl [6-(aminothiocarbonyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (3.26 g, 7 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (20 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was suspended in tetrahydrofuran (20 ml). To the obtained mixture were added triethylamine (2.0 ml, 14 mmol) and 9-fluorenylmethyl chloroformate (2.72 g, 10.5 mmol) and the mixture was stirred with heating at 0°C for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 9H-fluoren-9-ylmethyl [6-(aminocarbothioyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (3.21 g, 78.1%) as an amorphous.

¹H-NMR(CDCl₃) δ: 0.97 (6H, d, J=6.6 Hz), 2.07-2.24 (1H, m), 4.08 (2H, d, J=7.4 Hz), 4.19 (1H, t, J=6.8 Hz), 4.25 (2H, d, J=2.6 Hz), 4.41 (2H, d, J=6.8 Hz), 5.35 (1H, bs), 7.21-7.60 (13H, m), 7.72-7.76 (3H, m), 8.26 (1H, d, J=8.6 Hz).

(3) A suspension of 9H-fluoren-9-ylmethyl [6-(aminocarbothioyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.47 g, 0.8 mmol) and bromoacetone (0.22 g, 1.6 mmol) in ethanol (10 ml) was refluxed under heating for 1 h. The reaction mixture was poured into water and extracted with ethyl

acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 9H-fluoren-9-ylmethyl

⁵ [2-isobutyl-6-(4-methyl-1,3-thiazol-2-yl)-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.41 g, 82.0%) as an amorphous.

Elemental analysis for C₃₉H₃₅N₃O₃S 0.25H₂O

Calculated: C, 74.32; H, 5.68; N, 6.67.

¹⁰ Found: C, 74.36; H, 5.44; N, 6.62.

¹H-NMR(CDCl₃) δ: 1.00 (6H, d, J=6.8 Hz), 2.12-2.29 (1H, m), 2.44 (3H, d, J=0.8 Hz), 4.06 (2H, d, J=7.2 Hz), 4.19 (2H, t, J=6.6 Hz), 4.27 (2H, d, J=5.0 Hz), 4.44 (2H, d, J=6.6 Hz), 4.86 (1H, bs), 6.86 (1H, q, J=0.8 Hz), 7.26-

¹⁵ 7.44 (7H, m), 7.52-7.57 (5H, m), 7.75 (2H, d, J=7.0 Hz), 8.02 (1H, dd, J=1.8, 8.4 Hz), 8.50 (1H, d, J=8.4 Hz).

(4) To a solution of 9H-fluoren-9-ylmethyl [2-isobutyl-6-(4-methyl-1,3-thiazol-2-yl)-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.38 g, 0.6

²⁰ mmol) in N,N-dimethylformamide (10 ml) was added pyrrolidine (0.5 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The residue was purified by silica gel column chromatography

²⁵ to give 3-(aminomethyl)-2-isobutyl-6-(4-methyl-1,3-thiazol-2-yl)-4-phenyl-1(2H)-isoquinolinone (0.13 g, 54.2%) as crystals.

Melting point 162-163°C.

Elemental analysis for C₂₄H₂₄N₃OS 0.25H₂O

³⁰ Calculated: C, 70.64; H, 6.30; N, 10.30.

Found: C, 70.96; H, 6.38; N, 10.16.

¹H-NMR(CDCl₃) δ: 1.02 (6H, d, J=7.0 Hz), 1.35 (2H, bs), 2.13-2.35 (1H, m), 2.45 (3H, d, J=1.2 Hz), 3.69 (2H, s), 4.23 (2H, d, J=7.2 Hz), 6.85 (1H, q, J=1.2 Hz), 7.30-

³⁵ 7.35 (2H, m), 7.43 (1H, d, J=1.4 Hz), 7.48-7.59 (3H, m), 8.03 (1H, dd, J=1.4, 8.4 Hz), 8.52 (1H, d, J=8.4 Hz).

Example 195

Ethyl 2-[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylate hydrochloride

5 (1) A solution of 9H-fluoren-9-ylmethyl [6-(aminocarbothioyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (Example 194(2)) (2.35 g, 4 mmol) and ethyl bromopyruvate (1.56 g, 8 mmol) in ethanol (20 ml) was refluxed under heating for
10 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give
15 ethyl 2-[3-[[[(9H-fluoren-9-ylmethoxy)carbonyl]amino]methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylate (1.92 g, 70.3%) as crystals.

Melting point 151-152°C.

20 Elemental analysis for C₄₁H₃₇N₃O₅S

Calculated: C, 72.01; H, 5.45; N, 6.14.

Found: C, 71.79; H, 5.59; N, 6.02.

¹H-NMR(CDCl₃) δ: 1.00 (6H, d, J=6.6 Hz), 1.41 (3H, t, J=7.2 Hz), 2.16-2.27 (1H, m), 4.07 (2H, d, J=5.7 Hz),
25 4.19 (1H, t, J=6.6 Hz), 4.28 (2H, d, J=5.4 Hz), 4.38-4.45 (4H, m), 4.86 (1H, bs), 7.28-7.45 (7H, m), 7.75 (2H, d, J=7.1 Hz), 8.11 (1H, s), 8.13 (1H, dd, J=1.8, 8.4 Hz), 8.53 (1H, d, J=8.4 Hz).

(2) To a solution of ethyl 2-[3-[[[(9H-fluoren-9-ylmethoxy)carbonyl]amino]methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylate (1.84 g, 2.7 mmol) in N,N-dimethylformamide (20 ml) was added pyrrolidine (1 ml) and the mixture was stirred at room temperature for 1 h. The reaction
35 mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over

anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 ml) and di-t-butyl dicarbonate (0.9 ml, 4 mmol) was added thereto. The obtained mixture was 5 stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica 10 gel column chromatography to give ethyl 2-[3-[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylate (1.41 g, 93.4%) as crystals.
Melting point 170.5-171°C.

15 Elemental analysis for C₂₉H₃₉N₃O₆S
Calculated: C, 62.45; H, 7.05; N, 7.53.
Found: C, 62.50; H, 7.04; N, 7.53.
¹H-NMR(CDCl₃) δ: 1.02 (6H, d, J=6.6 Hz), 1.41 (3H, t, J=7.0 Hz), 1.44 (9H, s), 2.11-2.38 (1H, m), 4.19 (2H, d, J=7.2 Hz), 4.23 (2H, d, J=5.4 Hz), 4.42 (2H, q, J=7.0 Hz), 4.60 (1H, bs), 7.28-7.33 (2H, m), 7.45 (1H, d, J=1.8 Hz), 20 7.51-7.61 (3H, m), 8.11 (1H, s), 8.13 (1H, dd, J=1.8, 8.4 Hz), 8.52 (1H, d, J=8.4 Hz).
(3) Ethyl 2-[3-[(tert-butoxycarbonyl)amino]methyl]-2-
25 isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylate (0.17 g, 0.3 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was
30 concentrated under reduced pressure, and the precipitated crystals were recrystallized from methanol - diisopropyl ether to give ethyl 2-[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylate hydrochloride (0.13 g, 92.9%)
35 as crystals.
Melting point 265-267°C.

Elemental analysis for $C_{26}H_{28}N_3O_3ClS$ 0.5H₂O

Calculated: C, 61.59; H, 5.76; N, 8.29.

Found: C, 61.75; H, 5.77; N, 8.40.

¹H-NMR(DMSO-d₆) δ: 0.94 (6H, d, J=6.6 Hz), 1.30 (3H, t, J=7.2 Hz), 3.91 (2H, s), 4.11 (2H, d, J=7.2 Hz), 4.30 (2H, q, J=7.2 Hz), 7.46-7.50 (3H, m), 7.60-7.72 (3H, m), 8.15 (1H, dd, J=1.4, 8.4 Hz), 8.48 (1H, d, J=8.4 Hz), 8.59 (1H, s), 8.40 (3H, bs).

Example 196

¹⁰ 2-[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylic acid hydrochloride

(1) To a solution of ethyl 2-[3-[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylate (1.12 g, 2 mmol) in tetrahydrofuran (10 ml)-ethanol (10 ml) was added 1N sodium hydroxide (4 ml) and the mixture was stirred at room temperature for 2 h. The reaction mixture was poured into water, acidified with 1N

²⁰ hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give 2-[3-[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylic acid (1.02 g, 96.2%) as crystals.

Melting point 213-214°C.

Elemental analysis for $C_{29}H_{31}N_3O_5S$

³⁰ Calculated: C, 65.27; H, 5.86; N, 7.87.

Found: C, 65.01; H, 5.65; N, 7.65.

¹H-NMR(CDCl₃) δ: 1.02 (6H, d, J=6.6 Hz), 1.45 (9H, s), 2.18-2.34 (1H, m), 4.10 (2H, d, J=7.4 Hz), 4.23 (2H, d, J=5.2 Hz), 4.88 (1H, bs), 6.40 (1H, bs), 7.33-7.41 (3H, m), 7.47-7.58 (3H, m), 8.03 (1H, dd, J=1.8, 8.4 Hz), 8.21 (1H, s), 8.49 (1H, d, J=8.4 Hz).

(2) 2-[3-[(Tert-butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylic acid (0.16 g, 0.3 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was crystallized from ethyl acetate to give 2-[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylic acid hydrochloride (0.13 g, 92.9%) as crystals. Melting point 281-283°C.

Elemental analysis for C₂₄H₂₄N₃O₃ClS H₂O

Calculated: C, 59.07; H, 5.37; N, 8.61.

Found: C, 59.32; H, 5.42; N, 8.57.

¹H-NMR(DMSO-d₆) δ: 0.94 (6H, d, J=6.6 Hz), 2.01-2.21 (1H, m), 3.90 (2H, s), 4.10 (2H, d, J=7.8 Hz), 7.45-7.51 (3H, m), 7.56-7.64 (3H, m), 8.41 (1H, dd, J=1.7, 8.4 Hz), 8.48 (1H, d, J=8.4 Hz), 8.53 (1H, s), 8.57 (3H, bs).

20 Example 197

2-[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxamide hydrochloride

(1) A solution of 2-[3-[(tert-

25 butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylic acid (0.80 g, 1.5 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.58 g, 3 mmol) and 1-hydroxybenzotriazole ammonium salt (0.46 g,

30 3 mmol) in N,N-dimethylformamide (10 ml) was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from tetrahydrofuran - diisopropyl ether to give tert-

butyl[6-[4-(aminocarbonyl)-1,3-thiazol-2-yl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.75 g, 93.8%) as crystals.

⁵ Melting point 248-249°C.

Elemental analysis for C₂₉H₃₂N₄O₄S 0.25H₂O

Calculated: C, 64.84; H, 6.10; N, 10.43.

Found: C, 64.98; H, 6.21; N, 10.23.

¹H-NMR(CDCl₃) δ: 1.02 (6H, d, J=6.8 Hz), 1.44 (9H, s),

¹⁰ 2.19-2.34 (1H, m), 4.10 (2H, d, J=7.4 Hz), 4.24 (2H, d, J=5.4 Hz), 4.65 (1H, bs), 5.84 (1H, bs), 7.29-7.34 (2H, m), 7.44 (1H, d, J=1.8 Hz), 7.51-7.61 (3H, m), 8.00 (1H, dd, J=1.8, 8.4 Hz), 8.11 (1H, s), 8.52 (1H, d, J=8.4 Hz).

¹⁵ (2) Tert-butyl [6-[4-(aminocarbonyl)-1,3-thiazol-2-yl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]-methylcarbamate (0.32 g, 0.6 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room temperature for 1 h.

The reaction mixture was concentrated under reduced pressure and the residue was crystallized from ethyl acetate to give 2-[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxamide hydrochloride (0.27 g, 96.4%) as crystals.

Melting point 235-237°C.

²⁵ ¹H-NMR(DMSO-d₆) δ: 0.94 (6H, d, J=6.8 Hz), 2.05-2.21 (1H, m), 3.92 (2H, s), 4.10 (2H, d, J=7.8 Hz), 7.39 (1H, d, J=1.6 Hz), 7.45-7.50 (2H, m), 7.60-7.66 (3H, m), 7.70 (1H, bs), 7.79 (1H, bs), 8.28 (1H, d, J=1.6, 8.4 Hz), 8.30 (1H, s), 8.47 (1H, d, J=8.4 Hz), 8.58 (3H, bs).

³⁰ Example 198

2-[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carbonitrile hydrochloride

(1) A solution of tert-butyl [6-[4-(aminocarbonyl)-1,3-thiazol-2-yl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.32 g, 0.6 mmol) and

cyanuric chloride (0.33 g, 1.8 mmol) in N,N-dimethylformamide (10 mmol) was stirred at 0°C for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine,

- 5 dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [6-(4-cyano-1,3-thiazol-2-yl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.28 g,
- 10 90.3%) as crystals.

Melting point 209-211°C.

Elemental analysis for C₂₉H₃₀N₄O₃S

Calculated: C, 67.68; H, 5.88; N, 10.89.

Found: C, 67.72; H, 5.92; N, 10.62.

- 15 ¹H-NMR(CDCl₃) δ: 1.02 (6H, d, J=6.8 Hz), 1.44 (9H, s), 2.19-2.38 (1H, m), 4.10 (2H, d, J=7.8 Hz), 4.24 (2H, d, J=5.6 Hz), 4.58 (1H, bs), 7.28-7.32 (2H, m), 7.49 (1H, d, J=1.4 Hz), 7.52-7.63 (3H, m), 7.95 (1H, s), 7.96 (1H, dd, J=1.4, 8.4 Hz), 8.54 (1H, d, J=8.4 Hz).

- 20 (2) Tert-butyl [6-(4-cyano-1,3-thiazol-2-yl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.21 g, 0.4 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room

- 25 temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was crystallized from ethyl acetate to give 2-[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carbonitrile hydrochloride

- 30 (0.17 g, 94.4%) as crystals.

Melting point 274-276°C.

Elemental analysis for C₂₄H₂₃N₄OClS 0.5H₂O

Calculated: C, 62.67; H, 5.26; N, 12.18.

Found: C, 62.57; H, 5.06; N, 12.08.

- 35 ¹H-NMR(DMSO-d₆) δ: 0.94 (6H, d, J=6.6 Hz), 2.01-2.21 (1H, m), 3.89 (2H, m), 4.11 (2H, d, J=7.2 Hz), 7.45-7.51 (3H,

m), 7.61-7.64 (3H, m), 8.14 (1H, dd, J=1.8, 8.4 Hz), 8.48 (1H, d, J=8.4 Hz), 8.62 (3H, bs), 8.95 (1H, s).

Example 199

3-(Aminomethyl)-4-butoxy-2-isobutyl-6-(1H-pyrrol-1-yl)-

5 1(2H)-isoquinolinone dihydrochloride

(1) A solution of tert-butyl (6-amino-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-

isoquinolinyl)methylcarbamate (0.41 g, 1 mmol) and 2,5-dimethoxytetrahydrofuran (0.19 ml, 1.5 mmol) in acetic

10 acid (10 ml) was stirred at 80°C for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica

15 gel column chromatography to give tert-butyl [4-butoxy-2-isobutyl-1-oxo-6-(1H-pyrrol-1-yl)-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.31 g, 67.4%) as crystals.

Melting point 164-166°C.

20 Elemental analysis for C₂₇H₃₇N₃O₄

Calculated: C, 69.35; H, 7.98; N, 8.99.

Found: C, 69.29; H, 8.28; N, 8.87.

¹H-NMR(CDCl₃) δ: 0.97 (6H, d, J=6.6 Hz), 1.04 (3H, t, J=7.4 Hz), 1.47 (9H, s), 1.51-1.69 (2H, m), 1.81-1.95 (2H, m), 2.04-2.25 (1H, m), 3.89 (2H, t, J=6.5 Hz), 3.99 (2H, d, J=7.8 Hz), 4.53 (2H, d, J=5.6 Hz), 4.80 (1H, bs), 6.41-6.43 (2H, m), 7.21-7.23 (2H, m), 7.50-7.56 (1H, m), 7.62 (1H, d, J=1.8 Hz), 8.43-8.48 (1H, m).

(2) Tert-butyl [4-butoxy-2-isobutyl-1-oxo-6-(1H-pyrrol-1-yl)-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.23 g, 0.5 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the obtained crystals were recrystallized from methanol - diethyl ether to give 3-(aminomethyl)-4-butoxy-2-

isobutyl-6-(1H-pyrrol-1-yl)-1(2H)-isoquinolinone dihydrochloride (0.19 g, 95.0%) as crystals.

Melting point 156-157°C.

Elemental analysis for $C_{22}H_{30}N_3O_2Cl \cdot 0.5H_2O$

- ⁵ Calculated: C, 63.99; H, 7.57; N, 10.18.
 Found: C, 64.23; H, 7.86; N, 10.25.
¹H-NMR(DMSO-d₆) δ: 0.90 (6H, d, J=6.6 Hz), 1.00 (3H, t, J=7.3 Hz), 1.55-1.66 (2H, m), 1.81-2.13 (3H, m), 3.96-4.03 (4H, m), 4.19 (2H, bs), 6.39 (2H, t, J=2.2 Hz),
¹⁰ 7.55 (2H, t, J=2.2 Hz), 7.70 (1H, d, J=2.0 Hz), 7.89 (1H, dd, J=2.0, 8.8 Hz), 8.33 (1H, d, J=8.8 Hz), 8.72 (3H, bs).

Example 200

3-(Aminomethyl)-4-butoxy-2-isobutyl-6-(1H-tetrazol-1-

- ¹⁵ yl)-1(2H)-isoquinolinone hydrochloride
 (1) To a solution of tert-butyl (6-amino-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.41 g, 1 mmol) in acetic acid (5 ml) was added trimethyl orthoformate (0.33 ml, 3 mmol) and the mixture was stirred at room temperature for 30 min. To the obtained mixture was added sodium azide (0.10 g, 1.5 mmol) and the mixture was stirred at 80°C for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [4-butoxy-2-isobutyl-1-oxo-6-(1H-tetrazol-1-yl)-1,2-dihydro-3-isoquinolinyl]-
- ²⁰ methylcarbamate (0.31 g, 66.0%) as crystals.

Melting point 199-200°C.

¹H-NMR(CDCl₃) δ: 0.98 (6H, d, J=6.6 Hz), 1.05 (3H, t, J=7.3 Hz), 1.48 (9H, s), 1.54-1.69 (2H, m), 1.83-1.97 (2H, m), 2.12-2.26 (1H, m), 3.91 (2H, t, J=6.4 Hz), 4.03

- ³⁵ (2H, d, J=7.4 Hz), 4.56 (2H, d, J=5.4 Hz), 4.80 (1H, bs), 7.78 (1H, dd, J=2.2, 8.8 Hz), 8.09 (1H, d, J=2.2 Hz),

8.62 (1H, d, J=8.8 Hz), 9.15 (1H, s).

(2) Tert-butyl [4-butoxy-2-isobutyl-1-oxo-6-(1H-tetrazol-1-yl)-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.24 g, 0.5 mmol) was

5 dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the obtained crystals was crystallized from methanol - diethyl ether
10 to give 3-(aminomethyl)-4-butoxy-2-isobutyl-6-(1H-tetrazol-1-yl)-1(2H)-isoquinolinone hydrochloride (0.19 g, 95.0%) as crystals.

Melting point 177-179°C.

Elemental analysis for C₁₉H₂₇N₆O₂Cl 0.5H₂O

15 Calculated: C, 54.87; H, 6.79; N, 20.21.

Found: C, 55.08; H, 7.19; N, 20.00.

¹H-NMR(DMSO-d₆) δ: 0.91 (6H, d, J=6.6 Hz); 1.01 (3H, t, J=7.3 Hz), 1.43-1.67 (2H, m), 1.82-2.10 (3H, m), 3.98-4.04 (4H, m), 4.23 (2H, bs), 8.17 (1H, dd, J=2.0, 8.6 Hz),
20 8.23 (1H, d, J=2.0 Hz), 8.52 (1H, d, J=8.6 Hz), 8.73 (3H, bs), 10.38 (1H, s).

Example 201

3-(Aminomethyl)-4-butoxy-2-isobutyl-6-(1H-1,2,3-triazol-1-yl)-1(2H)-isoquinolinone hydrochloride

25 (1) To a solution of tert-butyl (6-amino-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.41 g, 1 mmol) in methanol (10 ml) was added N'-(2,2-dichloroethylidene)-4-methylbenzenesulfonohydrazide (0.28 g, 1 mmol) and the
30 mixture was stirred at 0°C for 1 h and at room temperature for 12 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [4-butoxy-2-isobutyl-

1-oxo-6-(1H-1,2,3-triazol-1-yl)-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.21 g, 45.7%) as crystals.

Melting point 190-191°C.

⁵ Elemental analysis for C₂₅H₃₅N₅O₄

Calculated: C, 63.97; H, 7.51; N, 14.91.

Found: C, 64.95; H, 7.69; N, 14.63.

¹H-NMR(CDCl₃) δ: 0.98 (6H, d, J=6.6 Hz), 1.04 (3H, t, J=7.0 Hz), 1.48 (9H, s), 1.54-1.69 (2H, m), 1.83-1.97

¹⁰ (2H, m), 2.04-2.24 (1H, m), 3.92 (2H, t, J=6.6 Hz), 4.02 (2H, d, J=7.8 Hz), 4.55 (2H, d, J=5.6 Hz), 4.82 (1H, bs), 7.81 (1H, dd, J=2.2, 8.8 Hz), 7.91 (1H, d, J=1.3 Hz), 8.12 (1H, d, J=1.3 Hz), 8.13 (1H, d, J=2.2 Hz), 8.56 (1H, d, J=8.8 Hz).

¹⁵ (2) tert-butyl [4-butoxy-2-isobutyl-1-oxo-6-(1H-1,2,3-triazol-1-yl)-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.14 g, 0.3 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room

²⁰ temperature for 1 h. The reaction mixture was concentrated under reduced pressure to give 3-(aminomethyl)-4-butoxy-2-isobutyl-6-(1H-1,2,3-triazol-1-yl)-1(2H)-isoquinolinone hydrochloride (81 mg, 62.3%) as an amorphous.

²⁵ ¹H-NMR(DMSO-d₆) δ: 0.91 (6H, d, J=6.6 Hz), 1.01 (3H, t, J=7.3 Hz), 1.49-1.68 (2H, m), 1.82-2.12 (3H, m), 3.89-4.03 (4H, m), 4.22 (2H, d, J=4.4 Hz), 8.09 (1H, d, J=1.3 Hz), 8.18 (1H, dd, J=2.0, 8.6 Hz), 8.24 (1H, d, J=2.0 Hz), 8.48 (1H, d, J=8.6 Hz), 8.75 (3H, bs), 9.11 (1H, d, J=1.3 Hz).

Example 202

3-(Aminomethyl)-4-butoxy-2-isobutyl-6-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-1(2H)-isoquinolinone hydrochloride

³⁵ (1) A solution of tert-butyl (4-butoxy-6-cyano-2-isobutyl-1-oxo-1,2-dihydro-3-

isoquinolinyl)methylcarbamate (0.85 g, 2 mmol), sodium carbonate (0.85 g, 8 mmol) and hydroxylamine hydrochloride (0.42 g, 6 mmol) in ethanol (20 ml) was refluxed with stirring for 12 h. The reaction mixture
5 was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [6-
10 [amino(hydroxyimino)methyl]-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.81 g, 88.0%) as crystals.
Melting point 209-210°C.
Elemental analysis for C₂₄H₃₆N₄O₅
15 Calculated: C, 62.59; H, 7.88; N, 12.16.
Found: C, 62.49; H, 7.93; N, 11.98.
¹H-NMR(CDCl₃) δ: 0.95 (6H, d, J=6.6 Hz), 1.02 (3H, t, J=7.3 Hz), 1.49-1.66 (11H, m), 1.78-1.91 (2H, m), 2.09-2.24 (1H, m), 3.68-3.84 (2H, m), 3.98 (2H, t, J=6.6 Hz),
20 4.51 (2H, d, J=4.8 Hz), 5.02 (2H, s), 5.16 (1H, bs), 5.37 (1H, bs), 7.62 (1H, d, J=8.3 Hz), 7.82 (1H, s), 8.25 (1H, d, J=8.3 Hz).
(2) To a solution of tert-butyl [6-
[amino(hydroxyimino)methyl]-4-butoxy-2-isobutyl-1-oxo-
25 1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.78 g, 1.7 mmol) in ethyl acetate (10 ml)- tetrahydrofuran (10 ml) was added 1,1'-carbonyldiimidazole (0.83 g, 5.1 mmol) and the mixture was stirred at 80°C for 2 h. The reaction mixture was poured into water and extracted
30 with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was crystallized from ethyl acetate - diisopropyl ether to give tert-butyl [4-butoxy-2-isobutyl-1-oxo-6-(5-oxo-4,5-dihydro-
35 1,2,4-oxadiazol-3-yl)-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.54 g, 65.9%) as

crystals.

Melting point 223-224°C.

Elemental analysis for $C_{25}H_{34}N_4O_6$ 0.25H₂O

Calculated: C, 61.15; H, 7.08; N, 11.41.

⁵ Found: C, 61.00; H, 7.11; N, 11.13.

¹H-NMR(CDCl₃) δ: 0.86 (6H, d, J=6.6 Hz), 0.98 (3H, t, J=7.3 Hz), 1.42 (9H, s), 1.43-1.61 (2H, m), 1.76-1.90 (2H, m), 2.04-2.15 (1H, m), 3.86-3.92 (4H, m), 4.39 (2H, d, J=4.4 Hz), 7.36 (1H, bs), 7.94 (1H, dd, J=1.4, 8.4

¹⁰ Hz), 8.15 (1H, d, J=1.4 Hz), 8.38 (1H, d, J=8.4 Hz).

(3) Tert-butyl [4-butoxy-2-isobutyl-1-oxo-6-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.44 g, 0.9 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl

¹⁵ acetate (10 ml) and the mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure and the obtained crystals were recrystallized from methanol - diethyl ether to give 3-(aminomethyl)-4-butoxy-2-isobutyl-6-(5-

²⁰ oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-1(2H)-isoquinolinone hydrochloride (0.36 g, 94.7%) as crystals.

Melting point 256-258°C.

Elemental analysis for $C_{20}H_{27}N_4O_4Cl$ 0.25H₂O

Calculated: C, 56.20; H, 6.49; N, 13.11.

²⁵ Found: C, 56.23; H, 6.65; N, 12.98.

¹H-NMR(DMSO-d₆) δ: 0.90 (6H, d, J=6.4 Hz), 1.01 (3H, t, J=7.3 Hz), 1.46-1.64 (2H, m), 1.83-2.16 (3H, m), 3.95-4.02 (4H, m), 4.21 (2H, s), 8.03 (1H, dd, J=1.8, 8.4 Hz), 8.21 (1H, d, J=1.8 Hz), 8.43 (1H, d, J=8.4 Hz), 8.68 (3H, bs).

Example 203

3-(Aminomethyl)-4-butoxy-2-isobutyl-6-(5-methyl-1,2,4-oxadiazol-3-yl)-1(2H)-isoquinolinone hydrochloride

(1) A solution of tert-butyl [6-

³⁵ [amino(hydroxyimino)methyl]-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.46 g, 1

mmol), acetic anhydride (0.14 ml, 1.5 mmol) and a catalytic amount of acetic acid in tetrahydrofuran (10 ml) was refluxed under heating for 10 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was crystallized from ethyl acetate - diisopropyl ether to give tert-butyl [4-butoxy-2-isobutyl-6-(5-methyl-1,2,4-oxadiazol-3-yl)-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.22 g, 45.8%) as crystals.

Melting point 151.5-152°C.

Elemental analysis for $C_{26}H_{36}N_4O_6$

Calculated: C, 64.44; H, 7.49; N, 11.56.

Found: C, 64.12; H, 7.74; N, 11.54.

1H -NMR(CDCl₃) δ : 0.98 (6H, d, J=6.6 Hz), 1.05 (3H, t, J=7.3 Hz), 1.47 (9H, s), 1.56-1.68 (2H, m), 1.86-1.95 (2H, m), 2.15-2.24 (1H, m), 2.70 (3H, s), 3.92 (2H, t, J=6.6 Hz), 4.02 (2H, d, J=7.5 Hz), 4.54 (2H, d, J=5.7

Hz), 4.78 (1H, bs), 8.15 (1H, dd, J=1.8, 8.7 Hz), 8.42 (1H, d, J=1.8 Hz), 8.51 (1H, d, J=8.7 Hz).

(2) Tert-butyl [4-butoxy-2-isobutyl-6-(5-methyl-1,2,4-oxadiazol-3-yl)-1-oxo-1,2-dihydro-3-isoquinolinyl]-methylcarbamate (0.15 g, 0.3 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure and the obtained crystals were recrystallized from methanol - diethyl ether to give 3-(aminomethyl)-4-butoxy-2-isobutyl-6-(5-methyl-1,2,4-oxadiazol-3-yl)-1(2H)-isoquinolinone hydrochloride (0.11 g, 91.7%) as crystals.

Melting point 230-232°C.

Elemental analysis for $C_{21}H_{29}N_4O_3Cl \cdot 0.25H_2O$

Calculated: C, 59.29; H, 6.99; N, 13.17.

Found: C, 59.50; H, 7.02; N, 12.95.

¹H-NMR(DMSO-d₆) δ: 0.90 (6H, d, J=6.6 Hz), 1.03 (3H, t, J=7.3 Hz), 1.52-1.67 (2H, m), 1.70-1.99 (2H, m), 2.02-2.12 (1H, m), 2.73 (3H, s), 3.95-4.02 (4H, m), 4.22 (2H, s), 8.18 (1H, d, J=8.4 Hz), 8.39 (1H, s), 8.45 (1H, d, J=8.4 Hz), 8.67 (3H, bs).

Example 204

3-(Aminomethyl)-4-butoxy-2-isobutyl-6-(1H-tetrazol-5-yl)-1(2H)-isoquinolinone hydrochloride

(1) A solution of tert-butyl (4-butoxy-6-cyano-2-
¹⁰ isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.85 g, 2 mmol), triethylamine hydrochloride (0.34 g, 2.5 mmol) and sodium azide (0.16 g, 2.5 mmol) in toluene (20 ml) was stirred at 90°C for 24 h. The reaction mixture was
¹⁵ poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from tetrahydrofuran - diisopropyl ether to give tert-
²⁰ butyl [4-butoxy-2-isobutyl-1-oxo-6-(1H-tetrazol-5-yl)-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.50 g, 53.2%) as crystals.

Melting point 152-153°C.

Elemental analysis for C₂₄H₃₄N₆O₄ 0.25H₂O

²⁵ Calculated: C, 60.68; H, 7.32; N, 17.69.

Found: C, 60.98; H, 7.20; N, 17.29.

¹H-NMR(CDCl₃) δ: 0.95-1.02 (9H, m), 1.48-1.61 (11H, m), 1.81-1.92 (2H, m), 2.14-2.27 (1H, m), 3.91 (2H, t, J=6.6 Hz), 4.08 (2H, d, J=7.2 Hz), 4.57 (2H, d, J=5.2 Hz),

³⁰ 4.79 (1H, bs), 5.39 (1H, bs), 8.12 (1H, dd, J=1.5, 8.5 Hz), 8.40 (1H, d, J=8.5 Hz), 8.46 (1H, d, J=1.5 Hz).

(2) Tert-butyl [4-butoxy-2-isobutyl-1-oxo-6-(1H-tetrazol-5-yl)-1,2-dihydro-3-

isoquinolinyl]methylcarbamate (0.47 g, 1 mmol) was

³⁵ dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room

temperature for 1 h. The reaction was concentrated under reduced pressure and the obtained crystals crystallized from methanol - diethyl ether to give 3-(aminomethyl)-4-butoxy-2-isobutyl-6-(1H-tetrazol-5-yl)-
5 1(2H)-isoquinolinone hydrochloride (0.38 g, 92.7%) as crystals.

Melting point 252-254°C.

Elemental analysis for C₁₉H₂₇N₆O₂Cl 0.25H₂O
Calculated: C, 55.47; H, 6.74; N, 20.43.
10 Found: C, 55.63; H, 6.67; N, 20.21.
¹H-NMR(DMSO-d₆) δ: 0.91 (6H, d, J=7.0 Hz), 1.02 (3H, t, J=7.3 Hz), 1.50-1.69 (2H, m), 1.85-2.10 (3H, m), 3.98-4.02 (4H, m), 4.22 (2H, s), 8.30 (1H, dd, J=1.4, 8.4 Hz), 8.48 (1H, d, J=8.4 Hz), 8.51 (1H, d, J=1.4 Hz), 8.63 (3H,
15 bs).

Example 205

2-(Aminomethyl)-4-isobutyl-5-phenyl[1,7]naphthyridin-8(7H)-one dihydrochloride

(1) To a suspension of 3-benzoylpyridin-2-carboxylic
20 acid (2.27 g, 10 mmol) in toluene (20 ml) was added thionyl chloride (0.88 ml, 12 mmol) and the mixture was stirred at 100°C for 2 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in tetrahydrofuran (20 ml). The obtained
25 solution was added dropwise to (isobutylamino)-acetonitrile (1.68 g, 15 mmol) in N,N-dimethylacetamide (20 ml) and the mixture was stirred at 70°C for 12 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine,
30 dried over anhydrous magnesium sulfate and concentrated under reduced pressure. To a solution of the residue and acetic anhydride (1.1 ml, 12 mmol) in acetonitrile (30 ml) was added 1,8-diazabicyclo[5.4.0]-7-undecene (6.0 ml, 40 mmol) at 0°C and the mixture was stirred at
35 room temperature for 15 h. Water was added to the reaction mixture and the mixture was stirred at room

temperature for 30 min. The precipitated crystals were collected by filtration. The obtained crystals were recrystallized from tetrahydrofuran - diisopropyl ether to give 7-isobutyl-8-oxo-5-phenyl-7,8-

5 dihydro[1,7]naphthyridine-6-carbonitrile (2.65 g, 87.5%) as crystals.

Melting point 221-222°C.

Elemental analysis for C₁₉H₁₇N₃O

Calculated: C, 75.23; H, 5.65; N, 13.85.

10 Found: C, 75.20; H, 5.72; N, 13.85.

¹H-NMR(CDCl₃) δ: 1.06 (6H, d, J=7.0 Hz), 2.30-2.51 (1H, m), 4.24 (2H, d, J=7.8 Hz), 7.37-7.46 (2H, m), 7.52-7.61 (4H, m), 7.72 (1H, dd, J=1.8, 8.3 Hz), 9.01 (1H, dd, J=1.8, 8.4 Hz).

15 (2) A suspension of 7-isobutyl-8-oxo-5-phenyl-7,8-dihydro[1,7]naphthyridine-6-carbonitrile (2.43 g, 8 mmol), Raney-cobalt (2.4 ml) and 25% aqueous ammonia (3.2 ml) in tetrahydrofuran (100 ml) was stirred under a hydrogen atmosphere at 5 atm and 60°C for 3 h. Raney-

20 cobalt was filtered off and the filtrate was concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (30 ml) and to the obtained solution was added di-t-butyl dicarbonate (2.3 ml, 10 mmol). The mixture was stirred at room temperature for

25 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give

30 tert-butyl (7-isobutyl-8-oxo-5-phenyl-7,8-dihydro[1,7]naphthyridin-6-yl)methylcarbamate (0.21 g, 6.4%) as crystals.

Melting point 176-177°C.

Elemental analysis for C₂₄H₂₉N₃O₃

35 Calculated: C, 70.74; H, 7.17; N, 10.31.

Found: C, 70.59; H, 7.18; N, 10.26.

¹H-NMR(CDCl₃) δ: 1.01 (6H, d, J=6.6 Hz), 1.44 (9H, s), 2.23-2.32 (1H, m), 4.14 (2H, d, J=7.2 Hz), 4.22 (2H, d, J=5.4 Hz), 4.93 (1H, bs), 7.26-7.33 (4H, m), 7.45-7.57 (3H, m), 8.76-8.77 (1H, m).

⁵ (3) Tert-butyl (7-isobutyl-8-oxo-5-phenyl-7,8-dihydro[1,7]naphthyridin-6-yl)methylcarbamate (0.16 g, 0.4 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 mL) and the mixture was stirred at room temperature for 1 h. The reaction ¹⁰ mixture was concentrated under reduced pressure and the obtained crystals were recrystallized from methanol - ethyl acetate to give 2-(aminomethyl)-4-isobutyl-5-phenyl[1,7]naphthyridin-8(7H)-one dihydrochloride (0.12 g, 80.0%) as crystals.

¹⁵ Melting point 293°C.

¹H-NMR(DMSO-d₆) δ: 0.94 (6H, d, J=6.6 Hz), 2.06-2.19 (1H, m), 3.91 (2H, d, J=3.9 Hz), 4.14 (2H, d, J=7.2 Hz), 7.41-7.44 (3H, m), 7.50-7.62 (3H, m), 7.71-7.76 (1H, m), 8.79 (3H, bs), 8.88-8.90 (1H, m).

²⁰ Example 206

3-(Aminomethyl)-2-isobutyl-6-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-4-phenyl-1(2H)-isoquinolinone hydrochloride

(1) To a mixture of tert-butyl (6-cyano-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.86 g, 2.0 mmol), hydroxylamine hydrochloride (0.21 g, 3.0 mmol) and ethanol (20 mL) was added potassium t-butoxide (0.34 g, 3.0 mmol) at room temperature and the mixture was stirred at 75-80°C for 3 h. The reaction ²⁵ mixture was poured into water (100 mL) and the mixture was extracted with ethyl acetate (50 mL). The organic layer was washed with saturated brine (20 mL) and dried over anhydrous magnesium sulfate (6 g). The solvent was evaporated and the residue was purified by silica gel ³⁰ mixture was poured into water (100 mL) and the mixture was extracted with ethyl acetate (50 mL). The organic layer was washed with saturated brine (20 mL) and dried over anhydrous magnesium sulfate (6 g). The solvent was evaporated and the residue was purified by column chromatography (n-hexane-ethyl acetate=1:1 (v/v)) to give tert-butyl {6-[amino(hydroxyimino)methyl]-2-

isobutyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl}methylcarbamate (0.57 g, 62%) as a colorless powder.

¹H-NMR(CDCl₃) δ: 0.90 (6H, d, J=6.6 Hz), 1.38 (9H, s), 2.05-2.20 (1H, m), 3.85-4.00 (4H, s), 5.84 (2H, bs),

5 7.29 (1H, d, J=1.8 Hz), 7.31 (1H, br), 7.35-7.55 (5H, m), 7.55 (1H, dd, J= 1.8, 8.4 Hz), 9.83 (1H, s).

(2) Tert-butyl {6-[amino(hydroxyimino)methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-

yl}methylcarbamate (0.25 g, 0.54 mmol) was dissolved in

10 ethyl acetate (10 mL) and N,N'-carbonyldiimidazole (0.26 g, 1.6 mmol) was added. The mixture was refluxed under heating for 3 h. To the reaction mixture were added 0.1 M aqueous citric acid solution (25 mL) and ethyl acetate (50 mL). The organic layer was washed with 0.1 M

15 aqueous citric acid solution (25 mL), and then saturated brine (25 mL), dried over anhydrous magnesium sulfate (12 g) and concentrated under reduced pressure. The residue was recrystallized from diisopropyl ether-ethyl acetate=2:1 (v/v) to give tert-butyl [2-isobutyl-1-oxo-

20 6-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.24 g, 93%) as a colorless powder.

¹H-NMR(CDCl₃) δ: 1.01 (6H, d, J=6.6 Hz), 1.44 (9H, s), 2.15-2.35 (1H, m), 4.10 (2H, d, J=7.2 Hz), 4.22 (2H, d,

25 J=5.4 Hz), 4.64 (1H, br), 7.25-7.35 (3H, m), 7.45-7.60 (3H, m), 7.82 (1H, dd, J=1.7, 8.4 Hz), 8.52 (1H, d, J=8.4 Hz).

(3) Tert-butyl [2-isobutyl-1-oxo-6-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-4-phenyl-1,2-dihydro-3-

30 isoquinolinyl]methylcarbamate (0.18 g, 0.37 mmol) was dissolved in ethanol (4 mL) and a solution (4 mL) of 4N hydrogen chloride in ethyl acetate was added. The mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure,

35 and the residue was washed with diisopropyl ether (2 mL) and recrystallized from ethyl acetate-ethanol (20:1) to

give 3-(aminomethyl)-2-isobutyl-6-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-4-phenyl-1(2H)-isoquinolinone hydrochloride (0.12 g, 80%) as a colorless powder.

Elemental analysis for $C_{22}H_{22}N_4O_3 \text{ HCl } 0.5H_2O$,

⁵ Calculated:C, 60.62; H, 5.55; N, 12.85.

Found: C, 61.01; H, 5.49; N, 12.21.

¹H-NMR(DMSO-d₆) δ: 0.93 (6H, d, J=6.6 Hz), 2.00-2.25 (1H, m), 3.88 (2H, s), 4.08 (2H, d, J=7.2 Hz), 7.35-7.45 (3H, m), 7.55-7.65 (3H, m), 7.96 (1H, dd, J=1.8, 8.4 Hz),

¹⁰ 8.46 (3H, br), 8.50 (1H, d, J=8.4 Hz).

Melting point: 253°C (decomposition)

Example 207

3-(Aminomethyl)-2-isobutyl-6-(5-oxo-4,5-dihydro-1,2,4-thiadiazol-3-yl)-4-phenyl-1(2H)-isoquinolinone

¹⁵ hydrochloride

(1) A mixture of tert-butyl {6-[amino(hydroxyimino)methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl}methylcarbamate (0.50 g, 1.1 mmol), acetic acid (5 mL) and acetic anhydride (0.12 mL,

²⁰ 1.3 mmol) was stirred at room temperature for 20 min.

To the reaction mixture was added 10% palladium-activated carbon (0.05 g) under a nitrogen atmosphere and the mixture was stirred at room temperature and 1 atm under a hydrogen atmosphere for 12 h. The insoluble

²⁵ material was filtered off and the solvent was evaporated.

Diisopropyl ether (2 mL) was added to the residue to give tert-butyl {6-[amino(imino)methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl}methylcarbamate diacetate (0.92 g, 85%) as a brown powder.

³⁰ ¹H-NMR(DMSO-d₆) δ: 0.90 (6H, d, J=6.6 Hz), 1.38 (9H, s), 1.80 (6H, s), 2.05-2.25 (1H, m), 3.90-4.05 (4H, m), 7.23 (1H, d, J=1.4 Hz), 7.30-7.45 (3H, m), 7.45-7.60 (3H, m), 7.76 (1H, dd, J=1.4, 8.2 Hz), 8.44 (1H, d, J=8.2 Hz), 10.59 (2H, br).

³⁵ (2) Chlorocarbonylsulfenyl chloride (0.04 mL, 0.45 mmol) was added to a mixture of tert-butyl {6-

[amino(imino)methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl)methylcarbamate diacetate (0.25 g, 0.43 mmol), sodium carbonate (0.40 g, 3.8 mmol), water (5 mL) and tetrahydrofuran (5 mL) while stirring 5 vigorously under ice-cooling. The reaction mixture was stirred for 3 h, warmed to room temperature and stirred for 1 h more. The reaction mixture was added to 1N hydrochloric acid (30 mL) and extracted twice with ethyl acetate (30 mL). The organic layers were combined and 10 washed with 1N hydrochloric acid (10 mL) and then saturated brine (10 mL), dried over anhydrous magnesium sulfate (12 g) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane-ethyl acetate=1:1 (v/v)) to give tert-butyl [2-isobutyl-1-oxo-6-(5-oxo-4,5-dihydro-1,2,4-thiadiazol-3-yl)-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.084 g, 39%) as a yellow powder.

¹H-NMR(CDCl₃) δ: 1.01 (6H, d, J=6.6 Hz), 1.44 (9H, s), 2.15-2.35 (1H, m), 4.03 (2H, d, J=6.6 Hz), 4.19 (2H, d, J=5.2 Hz), 4.73 (1H, br), 7.25-7.35 (3H, m), 7.50-7.60 (3H, m), 7.97 (1H, dd, J=1.8, 8.4 Hz), 8.53 (1H, d, J=8.4 Hz), 11.44 (1H, bs).

(3) Tert-butyl [2-isobutyl-1-oxo-6-(5-oxo-4,5-dihydro-1,2,4-thiadiazol-3-yl)-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.050 g, 0.10 mmol) was dissolved in tetrahydrofuran (3 mL) and a solution (2 mL) of 4N hydrogen chloride in ethyl acetate was added. The mixture was stirred at room temperature for 24 h.

30 The reaction mixture was concentrated under reduced pressure and diisopropyl ether-ethyl acetate (2:1) was added to the residue to give 3-(aminomethyl)-2-isobutyl-6-(5-oxo-4,5-dihydro-1,2,4-thiadiazol-3-yl)-4-phenyl-1(2H)-isoquinolinone hydrochloride (0.041 g, 94%) as a pale-yellow powder.

Elemental analysis for C₂₂H₂₂N₄O₂S HCl 0.75H₂O,

Calculated: C, 57.89; H, 5.41; N, 12.27.

Found: C, 57.95; H, 5.41; N, 11.58.

¹H-NMR(DMSO-d₆) δ: 0.95 (6H, d, J=6.6 Hz), 2.00-2.20 (1H, m), 3.93 (2H, s), 4.09 (2H, d, J=7.4 Hz), 7.35-7.50 (2H, m), 7.50-7.65 (3H, m), 7.86 (1H, d, J=1.8 Hz), 8.32 (1H, dd, J=1.8, 8.2 Hz), 8.48 (1H, d, J=8.2 Hz), 8.50 (3H, bs).

Melting point: 232-237°C

Example 208

¹⁰ 6-Bromo-2-isobutyl-1-oxo-4-phenyl-1,2-dihydroisoquinoline-3-carbonitrile

To a mixture of 2-benzoyl-4-bromobenzoic acid (5.0 g), toluene (65 ml) and dimethylformamide (0.1 ml) was added dropwise thionyl chloride (1.42 ml) under a nitrogen atmosphere, and the mixture was stirred at 50°C for 1.5 h. The solvent was evaporated and toluene (10 ml) was added to the residue. The mixture was heated to around 90°C. Diisopropylethylamine (4.21 ml) was added to the obtained solution and the mixture was stirred for about 5 min. Isobutylaminoacetonitrile (2.75 g) was added and the mixture was stirred at around the same temperature for 3 h. The reaction mixture was cooled to 25°C and 1N hydrochloric acid (50 ml) was added and stirred. The organic layer was separated and washed with 10% brine (50 ml). The solvent was evaporated to give 2-benzoyl-4-bromo-(N-cyanomethyl)-N-(isobutyl)benzamide. Acetonitrile (15 ml) and ethanol (15 ml) were added to the residue, and acetic anhydride (1.85 ml) and 1,8-diazabicyclo[5.4.0]-7-undecene (4.90 ml) were successively added dropwise to the mixture below 40°C. The reaction mixture was heated to 50°C and the mixture was stirred for 1 h. The reaction mixture was cooled to around 25°C and water (12.5 ml) was added dropwise. The mixture was stirred at the same temperature for 1 h. The precipitated crystals were collected by filtration and washed with 70% ethanol to

give the title compound (5.31 g, yield 85%).

¹H-NMR(300MHz, CDCl₃) δ:1.04(6H, d, J=6.7Hz), 2.30-2.39(1H, m), 4.15(2H, d, J=7.5Hz), 7.39-7.44(3H, m), 7.55-7.60(3H, m), 7.76(1H, dd, J=1.9Hz, 8.6Hz), 8.39(1H,
5 d, J=8.6Hz)

Example 209

3-(Aminomethyl)-6-bromo-2-isobutyl-4-phenylisoquinolin-1(2H)-one

A mixture of 6-bromo-2-isobutyl-1-oxo-4-phenyl-1,2-dihydroisoquinoline-3-carbonitrile (16.0 g), sponge cobalt (manufactured by Kawaken Fine Chemicals Co., Ltd.; trademark: ODHT-60) (4 ml), 25% ammonium hydroxide (2 ml) and tetrahydrofuran (80 ml) was stirred at 60°C at a 1 MPa hydrogen pressure for 4 h and the catalyst was filtered off. The solvent was evaporated and acetonitrile (48 ml) was added to the residue. The mixture was heated to about 70°C. The obtained solution was cooled to 25°C to give crystals, and water (80 ml) was added dropwise. The obtained mixture was cooled to around 5°C and the mixture was stirred for 1 h. The precipitated crystals were collected by filtration to give the title compound (14.8 g; yield 91.4%).

¹H-NMR(CDCl₃) δ:1.00(6H, d, J=6.7Hz), 1.10(2H, br), 2.25(1H, m), 3.65(2H, s), 4.20(2H, d, J=7.4Hz), 7.07(1H, d, J=1.9Hz), 7.08-7.28(2H, m), 7.45-7.54(4H, m), 8.32(1H, d, J=8.6Hz)

Example 210

3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydroisoquinoline-6-carbonitrile

A mixture of 3-(aminomethyl)-6-bromo-2-isobutyl-4-phenylisoquinolin-1(2H)-one (15.0 g), zinc cyanide (2.74 g), tetrakis(triphenylphosphine)palladium (1.35 g), N-methylpyrrolidone (75 ml) and water (0.75 ml) was stirred under a nitrogen atmosphere at an inner temperature of 54-56°C. To the reaction mixture was added dropwise saturated aqueous ammonium chloride-25%

ammonium hydroxide-water (4:1:4, 37.5 ml) over 30 min at the same temperature, and the mixture was stirred for 1 h and below 5°C for 1 h. The obtained crystals were collected by filtration and suspended in acetonitrile (105 ml). The suspension was dissolved at 80°C. To the obtained solution was added activated carbon (0.75 g) and the mixture was stirred for 10 min. The activated carbon was filtered off and washed with acetonitrile (15 ml). The filtrate was combined and cooled to 25°C to give crystals. Water (120 ml) was added dropwise and the obtained mixture was cooled to 5°C and stirred for 1 h. The obtained crystals were collected by filtration to give the title compound (9.6 g, yield 74.5%).

¹H-NMR(300MHz, CDCl₃) δ:1.01(6H, d, J=6.8Hz), 1.13(2H, br), 2.22-2.31(1H, m), 3.69(2H, s), 4.23(2H, d, J=7.5Hz), 5.55-5.95(2H, br), 7.24-7.28(3H, m), 7.50-7.56(3H, m), 7.61(1H, dd, J=1.5Hz, 8.3Hz), 8.55(1H, d, J=8.3Hz)

Example 211
3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydroisoquinoline-6-carboxamide 1/2 dimethyl sulfoxide solvate

A mixture of 3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydroisoquinoline-6-carbonitrile (20.0 g), 2N aqueous sodium hydroxide solution (6 ml), dimethyl sulfoxide (100 ml) and water (40 ml) was stirred at an inner temperature of 85°C for 30 min. The reaction mixture was cooled to 40°C, cooled to not higher than 5°C and stirred for 1 h. The precipitated crystals were collected by filtration and washed twice with water (40 ml) to give the title compound (21.7 g) as pale yellow crystals.

¹H-NMR(300MHz, CDCl₃) δ:1.01(6H, d, J=6.7Hz), 2.20-2.32(1H, m), 2.62(6H, s; DMSO), 3.68(2H, s), 4.24(2H, d, J=7.4Hz), 5.55-5.95(2H, br), 7.25-7.30(2H, m), 7.39(1H, d, J=1.6Hz), 7.45-7.55(3H, m), 7.79(1H, dd, J=1.5Hz, 8.3Hz), 8.54(1H, d, J=8.3Hz)

Example 212**3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydroisoquinoline-6-carboxamide**

A mixture of 3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydroisoquinoline-6-carboxamide (10 g), methanol (40 ml) and 1N hydrochloric acid (20 ml) was heated to 60°C. 1N Hydrochloric acid (ca. 7 ml) was added to the reaction mixture at around the same temperature to adjust pH to 2.0, and activated carbon (0.5 g) was added. The mixture was stirred for about 10 min and activated carbon was filtered off. The obtained solution was washed with methanol-water (2:1) (10 ml) and heated again to around 60°C with stirring. 5% Ammonium hydroxide was added to the reaction mixture while keeping the same temperature to adjust pH to 7.3, and water (10 ml) was added dropwise. The obtained mixture was cooled to 25°C, ice-cooled and stirred at around 5°C for 1 h. The precipitated crystals (8.48 g) were collected by filtration, suspended in ethyl acetate (85 ml) and stirred at around 75°C for 2 h. The obtained mixture was allowed to cool for 1 h, ice-cooled and stirred at around 5°C for 1 h. The precipitated crystals were collected by filtration and washed with previously-cooled ethyl acetate (17 ml) to give the title compound as crystals (8.02 g).

Powder X-ray crystal diffraction data

Diffraction angle: $2\theta(^{\circ})$ spacing: d value
(angstrom)

	8.96	9.86
30	13.7	6.46
	15.9	5.56
	16.6	5.34
	22.8	3.89
	24.4	3.65
35	24.7	3.60
	25.3	3.52

25.7

3.46

Example 213

7-(Aminomethyl)-6-isobutyl-8-phenyl[1,3]dioxolo[4,5-g]isoquinolin-5(6H)-one

5 This compound was synthesized according to the method similar to that in Example 106.

¹H-NMR(CDCl₃) δ: 0.99 (6H, d, J=6.6 Hz), 1.32 (2H, br), 2.26 (1H, m), 3.64 (2H, s), 4.19 (2H, d, J=7.6Hz), 6.00 (2H, s), 6.29 (1H, s), 7.23-7.28 (2H, m), 7.40-7.54 (3H, m), 7.83 (1H, s).

Example 214

Ethyl 2-[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-4-methyl-1,3-thiazole-5-carboxylate hydrochloride

15 (1) A solution of 9H-fluoren-9-ylmethyl [6-(aminocarbothioyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (1.76 g, 3 mmol) and ethyl 2-chloroacetate (0.99 g, 6 mmol) in ethanol (20 ml) was refluxed under heating for 12 h. The 20 reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give ethyl 2-[3- 25 {[[(9H-fluoren-9-ylmethoxy)carbonyl]amino)methyl}-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-4-methyl-1,3-thiazole-5-carboxylate (1.46 g, 69.9%) as crystals.

Melting point 157-158°C.

30 Elemental analysis for C₄₂H₃₉N₃O₅S

Calculated: C, 72.29; H, 5.63; N, 6.02.

Found: C, 72.12; H, 5.69; N, 5.79.

¹H-NMR(CDCl₃) δ: 0.99 (6H, d, J=6.9 Hz), 1.37 (3H, t, J=7.2 Hz), 2.12-2.29 (1H, m), 2.69 (3H, s), 4.08 (2H, d, J=6.0 Hz), 4.21 (1H, t, J=6.9 Hz), 4.26 (2H, d, J=4.8 Hz), 4.33 (2H, q, J=7.2 Hz), 4.44 (2H, d, J=6.9 Hz),

5.23 (1H, bs), 7.26-7.45 (7H, m), 7.51-7.60 (5H, m),
 7.75 (2H, d, J=7.5 Hz), 7.97 (1H, d, J=8.4 Hz), 8.46 (1H,
 d, J=8.4 Hz).

- (2) To a solution of ethyl 2-[3-{[(9H-fluoren-9-
 5 ylmethoxy)carbonyl]amino}methyl]-2-isobutyl-1-oxo-4-
 phenyl-1,2-dihydro-6-isoquinolinyl]-4-methyl-1,3-
 thiazole-5-carboxylate (1.40 g, 2 mmol) in N,N-
 dimethylformamide (20 ml) was added pyridine (1 ml).
 The mixture was stirred at room temperature for 1 h.
 10 The reaction mixture was poured into water and extracted
 with ethyl acetate. The extract was washed with brine,
 dried over anhydrous magnesium sulfate and concentrated
 under reduced pressure. The residue was dissolved in
 tetrahydrofuran (20 ml), and di-t-butyl dicarbonate
 15 (0.69 ml, 3 mmol) was added thereto. The resulting
 mixture was stirred at room temperature for 1 h. The
 reaction mixture was poured into water and extracted
 with ethyl acetate. The extract was washed with brine,
 dried over anhydrous magnesium sulfate and concentrated
 20 under reduced pressure. The residue was purified by
 silica gel column chromatography to give ethyl 2-(3-
 {[(tert-butoxycarbonyl)amino]methyl}-2-isobutyl-1-oxo-4-
 phenyl-1,2-dihydro-6-isoquinolinyl)-4-methyl-1,3-
 thiazole-5-carboxylate (0.88 g, 76.5%) as crystals.
 25 Melting point 201-202°C.
 Elemental analysis for C₃₀H₃₇N₃O₅S
 Calculated: C, 66.76; H, 6.48; N, 7.30.
 Found: C, 66.85; H, 6.56; N, 7.27.
¹H-NMR(CDCl₃) δ: 1.02 (6H, d, J=6.6 Hz), 1.37 (3H, t,
 30 J=7.0 Hz), 1.44 (9H, s), 2.18-2.32 (1H, m), 2.71 (3H, s),
 4.19 (2H, d, J=7.4 Hz), 4.22 (2H, d, J=5.6 Hz), 4.33 (2H,
 q, J=7.0 Hz), 4.69 (1H, bs), 7.28-7.34 (2H, m), 7.46 (1H,
 d, J=1.6 Hz), 7.51-7.62 (3H, m), 8.00 (1H, dd, J=1.6,
 8.4 Hz), 8.49 (1H, d, J=8.4 Hz).
 35 (3) Ethyl 2-(3-{[(tert-butoxycarbonyl)amino]methyl}-2-
 isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl)-4-

methyl-1,3-thiazole-5-carboxylate (0.14 g, 0.5 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The solution was stirred at room temperature for 1 h. The reaction mixture was 5 concentrated under reduced pressure, and the precipitated crystals were recrystallized from methanol - diisopropyl ether to give ethyl 2-[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-4-methyl-1,3-thiazole-5-carboxylate hydrochloride (0.11 g, 10 91.7%) as crystals.

Melting point 286-287°C.
Elemental analysis for $C_{27}H_{30}N_3O_3ClS$ 0.25H₂O
Calculated: C, 62.78; H, 5.95; N, 8.13.
Found: C, 62.94; H, 6.35; N, 8.11.
15 ¹H-NMR(DMSO-d₆) δ: 0.94 (6H, d, J=6.6 Hz), 1.29 (3H, t, J=7.2 Hz), 2.02-2.21 (1H, m), 2.63 (3H, s), 3.90 (2H, s), 4.10 (2H, d, J=7.8 Hz), 4.28 (2H, q, J=7.2 Hz), 7.44-7.52 (3H, m), 7.61-7.65 (3H, m), 8.14 (1H, dd, J=1.6, 8.4 Hz), 8.46 (1H, d, J=8.4 Hz), 8.59 (3H, bs).

20 Example 215
2-[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-4-methyl-1,3-thiazole-5-carboxylic acid hydrochloride
(1) To a solution of ethyl 2-[3-{[(tert-25 butoxycarbonyl)amino]methyl}-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-4-methyl-1,3-thiazole-5-carboxylate (0.69 g, 1.2 mmol) in tetrahydrofuran (10 ml) and ethanol (10 ml) was added 1N sodium hydroxide solution (3 ml). The resulting mixture was stirred at 30 room temperature for 2 h. The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was 35 crystallized from ethyl acetate - n-hexane to give 2-(3-{[(tert-butoxycarbonyl)amino]methyl}-2-isobutyl-1-oxo-4-

phenyl-1,2-dihydro-6-isoquinolinyl)-4-methyl-1,3-thiazole-5-carboxylic acid (0.61 g, 93.8%) as crystals.
Melting point 184-186°C.

Elemental analysis for C₃₀H₃₃N₃O₅S

5 Calculated: C, 65.79; H, 6.07; N, 7.67.

Found: C, 65.60; H, 6.23; N, 7.46.

¹H-NMR(CDCl₃) δ: 1.01 (6H, d, J=6.6 Hz), 1.50 (9H, s), 2.14-2.28 (1H, m), 2.67 (3H, s), 4.08 (2H, d, J=6.6 Hz), 4.17 (2H, s), 5.84 (1H, bs), 7.38-7.44 (2H, m), 7.51-10 7.71 (5H, m), 8.28 (1H, d, J=8.8 Hz).

(2) 2-(3-{[(Tert-butoxycarbonyl)amino]methyl}-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl)-4-methyl-1,3-thiazole-5-carboxylic acid (0.17 g, 0.3 mmol) was dissolved in a solution of 4N hydrogen chloride in 15 ethyl acetate (5 ml). The solution was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was crystallized from ethyl acetate to give 2-[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-20 isoquinolinyl]-4-methyl-1,3-thiazole-5-carboxylic acid hydrochloride (0.12 g, 92.3%) as crystals.
Melting point 239-241°C.

Elemental analysis for C₂₅H₂₆N₃O₃ClS H₂O

Calculated: C, 59.82; H, 5.62; N, 8.37.

25 Found: C, 59.64; H, 5.46; N, 8.08.

¹H-NMR(DMSO-d₆) δ: 0.94 (6H, d, J=6.6 Hz), 2.02-2.21 (1H, m), 2.61 (3H, s), 3.91 (2H, s), 4.10 (2H, d, J=8.8 Hz), 7.44-7.49 (3H, m), 7.61-7.66 (3H, m), 8.12 (1H, dd, J=1.4, 8.4 Hz), 8.45 (1H, d, J=8.4 Hz), 8.64 (3H, bs).

30 Example 216

2-[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-4-methyl-1,3-thiazole-5-carboxamide hydrochloride

(1) A solution of 2-(3-{[(tert-

35 butoxycarbonyl)amino]methyl}-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl)-4-methyl-1,3-thiazole-5-

carboxylic acid (0.44 g, 0.8 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.31 g, 1.6 mmol) and 1-hydroxybenzotriazole ammonium salt (0.24 g, 1.6 mmol) in N,N-dimethylformamide (10 ml) was
5 stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting crystals were
10 recrystallized from ethyl acetate - diisopropyl ether to give tert-butyl {6-[5-(aminocarbonyl)-4-methyl-1,3-thiazol-2-yl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl}methylcarbamate (0.38 g, 86.4%) as crystals.

15 Melting point 227-228°C.

Elemental analysis for C₃₀H₃₄N₄O₄S

Calculated: C, 65.91; H, 6.27; N, 10.25.

Found: C, 65.70; H, 6.19; N, 10.35.

¹H-NMR(CDCl₃) δ: 1.01 (6H, d, J=6.4 Hz), 1.45 (9H, s),
20 2.12-2.31 (1H, m), 2.66 (3H, s), 4.08 (2H, d, J=7.4 Hz),
4.20 (2H, d, J=5.2 Hz), 5.00 (1H, bs), 5.84 (2H, bs),
7.31-7.37 (3H, m), 7.52-7.61 (3H, m), 7.92 (1H, dd,
J=1.6, 8.4 Hz), 8.41 (1H, d, J=8.4 Hz)..

(2) Tert-butyl {6-[5-(aminocarbonyl)-4-methyl-1,3-thiazol-2-yl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl}methylcarbamate (0.14 g, 0.25 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The solution was stirred at room temperature for 1h. The reaction was concentrated under reduced pressure, and the resulting crystals were
30 recrystallized from methanol - ethyl acetate to give 2-[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-4-methyl-1,3-thiazole-5-carboxamide hydrochloride (0.11 g, 91.7%) as crystals.

35 Melting point 222-224°C.

¹H-NMR(DMSO-d₆) δ: 0.94 (6H, d, J=6.6 Hz), 2.02-2.21 (1H,

m), 2.56 (3H, s), 3.89 (2H, s), 4.10 (2H, d, J=6.4 Hz), 7.42-7.49 (3H, m), 7.61-7.78 (5H, m), 8.09 (1H, d, J=8.6 Hz), 8.46 (1H, d, J=8.6 Hz), 8.54 (3H, bs).

Example 217

- 5 2-[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-4-methyl-1,3-thiazole-5-carbonitrile hydrochloride
 (1) A solution of tert-butyl {6-[5-(aminocarbonyl)-4-methyl-1,3-thiazol-2-yl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl}methylcarbamate (0.16 g, 0.3 mmol) and cyanuric chloride (0.17 g, 0.9 mmol) in N,N-dimethylformamide (10 mmol) was stirred at 0°C for 1h. The resulting reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [6-(5-cyano-4-methyl-1,3-thiazol-2-yl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.15 g, 93.8%) as crystals.

Melting point 209-211°C.

Elemental analysis for C₃₀H₃₂N₄O₃S

Calculated: C, 68.16; H, 6.10; N, 10.60.

25 Found: C, 68.17; H, 5.99; N, 10.70.

- ¹H-NMR(CDCl₃) δ: 1.04 (6H, d, J=6.6 Hz), 1.44 (9H, s), 2.14-2.36 (1H, m), 2.61 (3H, s), 4.10 (2H, d, J=7.2 Hz), 4.23 (2H, d, J=5.4 Hz), 4.63 (1H, bs), 7.27-7.32 (2H, m), 7.42 (1H, d, J=1.5 Hz), 7.53-7.60 (3H, m), 7.97 (1H, dd, J=1.5, 8.4 Hz), 8.52 (1H, d, J=8.4 Hz).
 (2) Tert-butyl [6-(5-cyano-4-methyl-1,3-thiazol-2-yl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.21 g, 0.4 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The solution was stirred at room temperature for 1 h. The reaction mixture was

concentrated under reduced pressure, and the residue was crystallized from ethyl acetate to give 2-[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-4-methyl-1,3-thiazole-5-carbonitrile

5 hydrochloride (0.11 g, 91.7%) as crystals.

Melting point 284-285°C.

Elemental analysis for C₂₅H₂₅N₄OClS 0.25H₂O

Calculated: C, 63.95; H, 5.47; N, 11.93.

Found: C, 64.00; H, 5.45; N, 11.73.

10 ¹H-NMR(DMSO-d₆) δ: 0.94 (6H, d, J=6.6 Hz), 2.06-2.21 (1H, m), 2.54 (3H, s), 3.89 (2H, s), 4.11 (2H, d, J=7.6 Hz), 7.44-7.49 (2H, m), 7.52 (1H, d, J=1.5 Hz), 7.60-7.63 (3H, m), 8.11 (1H, dd, J=1.5, 8.4 Hz), 8.48 (1H, d, J=8.4 Hz), 8.63 (3H, bs).

15 Example 218

Ethyl 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-4-methyl-1,3-thiazole-5-carboxylate hydrochloride

(1) A solution of 9H-fluoren-9-ylmethyl [6-(aminocarbothioyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (2.33 g, 4 mmol) and ethyl 2-chloroacetate (1.32 g, 8 mmol) in ethanol (20 ml) was refluxed under heating for 10 h. The resulting reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give ethyl 2-[4-butoxy-3-((9H-fluoren-9-

30 ylmethoxy)carbonyl]amino)methyl]-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-4-methyl-1,3-thiazole-5-carboxylate (1.81 g, 65.3%) as crystals.

Melting point 203-204°C.

Elemental analysis for C₄₀H₄₃N₃O₆S

35 Calculated: C, 69.24; H, 6.25; N, 6.06.

Found: C, 69.08; H, 6.11; N, 5.99.

¹H-NMR(CDCl₃) δ: 0.97 (6H, d, J=6.6 Hz), 1.07 (3H, t, J=7.2 Hz), 1.42 (3H, t, J=7.2 Hz), 1.58-1.75 (2H, m), 1.84-1.97 (2H, m), 2.04-2.23 (1H, m), 2.81 (3H, s), 3.92 (2H, t, J=6.4 Hz), 4.00 (2H, d, J=7.2 Hz), 4.23 (1H, t, J=6.8 Hz), 4.39 (2H, q, J=7.2 Hz), 4.49 (2H, d, J=6.8 Hz), 4.59 (2H, d, J=5.6 Hz), 5.29 (1H, bs), 7.28-7.43 (4H, m), 7.60 (2H, d, J=7.4 Hz), 7.75 (2H, d, J=7.0 Hz), 8.05 (1H, dd, J=1.8, 8.4 Hz), 8.24 (1H, d, J=1.8 Hz), 8.44 (1H, d, J=8.4 Hz).

10 (2) To a solution of ethyl 2-[4-butoxy-3-({[(9H-fluoren-9-ylmethoxy)carbonyl]amino}methyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-4-methyl-1,3-thiazole-5-carboxylate (1.73 g, 2.5 mmol) in N,N-dimethylformamide (20 ml) and tetrahydrofuran (10 ml) was added

15 pyrrolidine (2 ml). The resulting mixture was stirred at room temperature for 1 h. The reaction was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 ml), and di-t-butyl dicarbonate (0.9 ml, 3.8 mmol) was added thereto. The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give ethyl 2-(4-butoxy-3-{[(tert-butoxycarbonyl)amino]methyl}-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl)-4-methyl-1,3-thiazole-5-carboxylate (1.15 g, 80.4%) as crystals.

20 Melting point 145.5-147°C.
Elemental analysis for C₃₀H₄₁N₃O₆S
Calculated: C, 63.02; H, 7.23; N, 7.35.
30 Found: C, 63.00; H, 7.30; N, 7.28.

35 ¹H-NMR(CDCl₃) δ: 0.97 (6H, d, J=6.6 Hz), 1.08 (3H, t,

J=7.3 Hz), 1.41 (3H, t, J=7.2 Hz), 1.47 (9H, s), 1.57-1.76 (2H, m), 1.85-1.99 (2H, m), 2.08-2.24 (1H, m), 2.81 (3H, s), 3.92 (2H, t, J=6.4 Hz), 4.00 (2H, d, J=7.8 Hz), 4.38 (2H, q, J=7.2 Hz), 4.54 (2H, d, J=5.6 Hz), 4.87 (1H, bs), 8.05 (1H, dd, J=1.8, 8.6 Hz), 8.26 (1H, d, J=1.8 Hz), 8.46 (1H, d, J=8.6 Hz).

(3) Ethyl 2-(4-butoxy-3-{{(tert-butoxycarbonyl)amino)methyl}-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl)-4-methyl-1,3-thiazole-5-carboxylate (0.17 g, 0.3 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The solution was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was crystallized from ethyl acetate to give ethyl 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-4-methyl-1,3-thiazole-5-carboxylate hydrochloride (0.14 g, 93.3%) as crystals.

Melting point 250-254°C.

Elemental analysis for C₂₅H₃₄N₃O₄ClS

Calculated: C, 59.10; H, 6.75; N, 8.27.

Found: C, 58.90; H, 6.84; N, 8.25.

¹H-NMR(DMSO-d₆) δ: 0.90 (6H, d, J=6.6 Hz), 1.05 (3H, t, J=7.1 Hz), 1.33 (3H, t, J=7.0 Hz), 1.57-1.76 (2H, m), 1.82-1.95 (2H, m), 2.00-2.18 (1H, m), 2.74 (3H, s), 3.97-4.00 (4H, m), 4.21 (2H, s), 4.33 (2H, q, J=7.0 Hz), 8.18 (1H, d, J=8.4 Hz), 8.32 (1H, s), 8.39 (1H, d, J=8.4 Hz), 8.67 (3H, bs).

Example 219

2-[3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-4-methyl-1,3-thiazole-5-carboxylic acid hydrochloride

(1) To a solution of ethyl 2-(4-butoxy-3-{{(tert-butoxycarbonyl)amino)methyl}-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl)-4-methyl-1,3-thiazole-5-carboxylate (0.91 g, 1.6 mmol) in tetrahydrofuran (5 ml)

and ethanol (5 ml) was added 1N sodium hydroxide solution (3 ml). The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting crystals were recrystallized from ethyl acetate - diisopropyl ether to give 2-(4-butoxy-3-{{(tert-
10 butoxycarbonyl)amino}methyl}-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl)-4-methyl-1,3-thiazole-5-carboxylic acid (0.78 g, 89.7%) as crystals.
Melting point 107-109°C.
Elemental analysis for $C_{28}H_{37}N_3O_6S \cdot 0.5H_2O$:
Calculated: C, 60.85; H, 6.93; N, 7.60.
Found: C, 60.73; H, 6.92; N, 7.41.
 1H -NMR(CDCl₃) δ: 0.96 (6H, d, J=6.6 Hz), 1.11 (3H, t, J=7.3 Hz), 1.52 (9H, s), 1.60-1.78 (2H, m), 1.87-2.01 (2H, m), 2.04-2.21 (1H, m), 2.82 (3H, s), 3.89-3.98 (4H, m), 4.54 (2H, d, J=4.8 Hz), 5.71 (1H, bs), 7.91 (1H, d, J=8.3 Hz), 8.10 (1H, s), 8.29 (1H, d, J=8.3 Hz).
(2) 2-(4-Butoxy-3-{{(tert-butoxycarbonyl)amino}methyl}-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl)-4-methyl-1,3-thiazole-5-carboxylic acid (0.16 g, 0.3 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The solution was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was crystallized from ethyl acetate to give 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-4-methyl-1,3-thiazole-5-carboxylic acid hydrochloride (0.13 g, 92.9%) as crystals.
Melting point 275-276°C.
Elemental analysis for. Calcd for $C_{23}H_{30}N_3O_4ClS \cdot 0.25H_2O$:
Calculated: C, 57.01; H, 6.34; N, 8.67.
Found: C, 57.03; H, 6.28; N, 8.51.

¹H-NMR(DMSO-d₆) δ: 0.90 (6H, d, J=6.6 Hz), 1.05 (3H, t, J=7.4 Hz), 1.59-1.72 (2H, m), 1.83-1.91 (2H, m), 1.99-2.16 (1H, m), 2.72 (3H, s), 3.98-4.06 (4H, m), 4.21 (2H, s), 8.18 (1H, d, J=8.1 Hz), 8.31 (1H, s), 8.39 (1H, d, J=8.1 Hz), 8.65 (3H, bs).

Example 220

2-[3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-4-methyl-1,3-thiazole-5-carboxamide hydrochloride

(1) A solution of 2-(4-butoxy-3-{[(tert-butoxycarbonyl)amino]methyl}-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl)-4-methyl-1,3-thiazole-5-carboxylic acid (0.60 g, 1.1 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.42 g, 2.2 mmol) and 1-hydroxybenzotriazole ammonium salt (0.33 g, 2.2 mmol) in N,N-dimethylformamide (10 ml) was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting crystals were recrystallized from tetrahydrofuran - diisopropyl ether to give tert-butyl {6-[5-(aminocarbonyl)-4-methyl-1,3-thiazol-2-yl]-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl}methylcarbamate (0.58 g, 96.7%) as crystals.

Melting point 233.5-234°C.

Elemental analysis for C₂₈H₃₈N₄O₄S

Calculated: C, 61.97; H, 7.06; N, 10.32.

Found: C, 61.95; H, 7.07; N, 10.19.

¹H-NMR(CDCl₃) δ: 0.97 (6H, d, J=6.6 Hz), 1.07 (3H, t, J=7.3 Hz), 1.49 (9H, s), 1.55-1.71 (2H, m), 1.80-1.98 (2H, m), 2.05-2.24 (1H, m), 2.78 (3H, s), 3.91 (2H, t, J=6.4 Hz), 3.99 (2H, d, J=7.4 Hz), 4.53 (2H, d, J=5.0 Hz), 5.05 (1H, bs), 5.94 (2H, bs), 7.98 (1H, dd, J=1.6, 8.6 Hz), 8.19 (1H, d, J=1.6 Hz), 8.42 (1H, d, J=8.6 Hz).

(2) Tert-butyl {6-[5-(aminocarbonyl)-4-methyl-1,3-thiazol-2-yl]-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl}methylcarbamate (0.22 g, 0.4 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The solution was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was crystallized from ethyl acetate to give 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-4-methyl-1,3-thiazole-5-carboxamide hydrochloride (0.18 g, 94.7%) as crystals.

Melting point 270-271°C.

Elemental analysis for C₂₃H₃₁N₄O₃ClS

Calculated: C, 57.67; H, 6.52; N, 11.70.

Found: C, 57.37; H, 6.46; N, 11.62.

¹H-NMR(DMSO-d₆) δ: 0.90 (6H, d, J=6.6 Hz), 1.05 (3H, t, J=7.1 Hz), 1.56-1.74 (2H, m), 1.82-2.18 (3H, m), 2.67 (3H, s), 3.97-4.00 (4H, m), 4.21 (2H, s), 7.77 (2H, bs), 8.27 (1H, d, J=1.5 Hz), 8.39 (1H, dd, J=1.5, 8.4 Hz), 8.39 (1H, d, J=8.4 Hz), 8.66 (3H, bs).

Example 221

2-[3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-4-methyl-1,3-thiazole-5-carbonitrile hydrochloride

(1) A solution of tert-butyl {6-[5-(aminocarbonyl)-4-methyl-1,3-thiazol-2-yl]-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl}methylcarbamate (0.33 g, 0.6 mmol) and cyanuric chloride (0.33 g, 1.8 mmol) in N,N-dimethylformamide (10 mmol) was stirred for 1h at 0°C.

The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [4-butoxy-6-(5-cyano-4-methyl-1,3-thiazol-2-yl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.25

g, 80.6%) as crystals.

Melting point 148.5-149.5°C.

Elemental analysis for C₂₈H₃₆N₄O₄S

Calculated: C, 64.10; H, 6.92; N, 10.68.

5 Found: C, 64.04; H, 6.96; N, 10.63.

¹H-NMR(CDCl₃) δ: 0.98 (6H, d, J=6.6 Hz), 1.08 (3H, t, J=7.3 Hz), 1.47 (9H, s), 1.57-1.75 (2H, m), 1.84-1.98 (2H, m), 2.08-2.28 (1H, m), 2.72 (3H, s), 3.91 (2H, t, J=6.4 Hz), 4.01 (2H, d, J=7.4 Hz), 4.54 (2H, d, J=5.6 Hz), 4.80 (1H, bs), 8.02 (1H, dd, J=1.8, 8.2 Hz), 8.24 (1H, d, J=1.8 Hz), 8.48 (1H, d, J=8.2 Hz).

(2) Tert-butyl [4-butoxy-6-(5-cyano-4-methyl-1,3-thiazol-2-yl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.21 g, 0.4 mmol) was

15 dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The solution was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was crystallized from ethyl acetate - diisopropyl ether to give 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-4-methyl-1,3-thiazole-5-carbonitrile hydrochloride (0.17 g, 94.4%) as crystals.

Melting point 166-168°C.

Elemental analysis for C₂₃H₂₉N₄O₂ClS 0.5H₂O

25 Calculated: C, 58.77; H, 6.43; N, 11.92.

Found: C, 58.58; H, 6.45; N, 11.91.

¹H-NMR(DMSO-d₆) δ: 0.90 (6H, d, J=6.6 Hz), 1.04 (3H, t, J=7.4 Hz), 1.55-1.73 (2H, m), 1.82-1.95 (2H, m), 1.98-2.16 (1H, m), 2.66 (3H, s), 3.98-4.01 (4H, m), 4.22 (2H, s), 8.17 (1H, dd, J=1.8, 8.4 Hz), 8.30 (1H, d, J=1.8 Hz), 8.42 (1H, d, J=8.4 Hz), 8.69 (3H, bs).

Example 222

3-(Aminomethyl)-6-(4-amino-1,3-thiazol-2-yl)-2-isobutyl-4-phenyl-1(2H)-isoquinolinone dihydrochloride

35 (1) A solution of 2-(3-{[(tert-butoxycarbonyl)amino]methyl}-2-isobutyl-1-oxo-4-phenyl-

1,2-dihydro-6-isoquinolinyl)-1,3-thiazole-4-carboxylic acid (1.60 g, 3 mmol), diphenylphosphoryl azide (0.78 ml, 3.6 mmol) and triethylamine (0.50 ml, 3.6 mmol) in N,N-dimethylformamide (10 ml) was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in toluene (20 ml) and refluxed for 1 h. To the resulting mixture was added 9-fluorenylmethanol (0.88 g, 4.5 mmol), and the mixture was stirred at 100°C for 3 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 9H-fluoren-9-ylmethyl 2-(3-[(tert-butoxycarbonyl)amino]methyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl)-1,3-thiazol-4-ylcarbamate (1.12 g, 51.4%) as an amorphous solid.

¹H-NMR(CDCl₃) δ: 1.01 (6H, d, J=6.6 Hz), 1.44 (9H, s), 2.19-2.32 (1H, m), 4.07 (2H, d, J=6.6 Hz), 4.11-4.22 (3H, m), 4.45 (2H, s), 4.63 (1H, bs), 7.24-7.56 (13H, m), 7.77 (2H, d, J=7.5 Hz), 7.88 (1H, d, J=7.8 Hz), 7.97 (1H, bs), 8.47 (1H, d, J=7.8 Hz).

(2) To a solution of 9H-fluoren-9-ylmethyl 2-(3-[(tert-butoxycarbonyl)amino]methyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl)-1,3-thiazol-4-ylcarbamate (1.09 g, 1.5 mmol) in N,N-dimethylformamide (20 ml) was added pyrrolidine (1 ml). The mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [6-(4-amino-1,3-

thiazol-2-yl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.59 g, 78.7%) as crystals.

Melting point 195-196°C.

5 Elemental analysis for $C_{28}H_{32}N_4O_3S$ 0.25H₂O

Calculated: C, 66.05; H, 6.43; N, 11.00.

Found: C, 66.20; H, 6.54; N, 10.96.

¹H-NMR(CDCl₃) δ: 1.01 (6H, d, J=6.6 Hz), 1.43 (9H, s), 1.98-2.35 (1H, m), 4.08 (2H, d, J=7.8 Hz), 4.14 (2H, bs), 10 4.21 (2H, d, J=5.8 Hz), 4.58 (1H, bs), 5.95 (1H, s), 7.27-7.31 (2H, m), 7.42 (1H, d, J=1.6 Hz), 7.48-7.59 (3H, m), 7.91 (1H, dd, J=1.6, 8.2 Hz), 8.47 (1H, d, J=8.2 Hz).

(3) Tert-butyl [6-(4-amino-1,3-thiazol-2-yl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-

15 isoquinolinyl]methylcarbamate (0.14 g, 0.5 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The solution was stirred at room temperature for 1 h. The reaction was concentrated under reduced pressure, and the residue was crystallized

20 from ethyl acetate to give 3-(aminomethyl)-6-(4-amino-1,3-thiazol-2-yl)-2-isobutyl-4-phenyl-1(2H)-isoquinolinone dihydrochloride (0.13 g, 92.9%) as crystals.

Melting point 230°C.

25 ¹H-NMR(DMSO-d₆) δ: 0.94 (6H, d, J=6.2 Hz), 1.99-2.21 (1H, m), 3.87 (2H, s), 4.10 (2H, d, J=8.2 Hz), 5.48 (3H, bs), 7.10 (1H, s), 7.16-7.62 (6H, m), 8.03 (1H, d, J=8.4 Hz), 8.44 (1H, d, J=8.4 Hz), 8.67 (3H, bs).

Example 223

30 N-{2-[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-1,3-thiazol-4-yl}acetamide hydrochloride

(1) A solution of tert-butyl [6-(4-amino-1,3-thiazol-2-yl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-

35 isoquinolinyl]methylcarbamate (0.20 g, 0.4 mmol) and acetyl chloride (0.04 ml, 0.6 mmol) in N,N-

dimethylacetamide (10 ml) was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl {6-[4-(acetylamino)-1,3-thiazol-2-yl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl}methylcarbamate (0.18 g, 85.7%) as crystals.

Melting point 227-228°C.

Elemental analysis for $C_{30}H_{34}N_4O_4S$

Calculated: C, 65.91; H, 6.27; N, 10.25.

Found: C, 65.66; H, 6.44; N, 10.17.

¹⁵ $^1\text{H-NMR}(\text{CDCl}_3)$ δ: 0.99 (6H, d, J=6.6 Hz), 1.47 (9H, s), 2.18-2.39 (4H, m), 4.10 (2H, bs), 4.19 (2H, bs), 7.06-7.38 (4H, m), 7.41-7.56 (3H, m), 7.61 (1H, s), 8.13 (1H, bs), 8.69 (1H, bs).

(2) Tert-butyl {6-[4-(acetylamino)-1,3-thiazol-2-yl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl}methylcarbamate (0.14 g, 0.25 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The solution was stirred at room temperature for 1 h. The reaction was concentrated under reduced pressure, and the residue was crystallized from ethyl acetate to give N-{2-[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-1,3-thiazol-4-yl}acetamide hydrochloride (0.11 g, 91.7%) as crystals.

³⁰ Melting point 242-244°C.

Elemental analysis for $C_{25}H_{27}N_4O_2ClS \cdot 2H_2O$

Calculated: C, 57.85; H, 6.02; N, 10.79.

Found: C, 57.70; H, 5.69; N, 10.69.

³⁵ $^1\text{H-NMR}(\text{DMSO}-d_6)$ δ: 0.93 (6H, d, J=6.6 Hz), 1.99-2.18 (4H, m), 3.86 (2H, s), 4.10 (2H, d, J=6.3 Hz), 7.45-7.48 (3H, m), 7.54-7.66 (4H, m), 8.05 (1H, d, J=8.6 Hz), 8.46 (1H,

d, J=8.6 Hz), 8.65 (3H, bs), 11.03 (1H, s).

Example 224

Methyl 2-{{[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]oxy}-2-methylpropanoate

5 hydrochloride

(1) To a solution of tert-butyl [6-hydroxy-2-isobutyl-4-phenyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.42 g, 1 mmol) in N,N-dimethylformamide (10 ml) was added sodium hydride (48 mg, 1.2 mmol) (60% in oil). The resulting mixture was stirred at 0°C for 10 min. To the mixture was added methyl 2-bromoisobutyrate (0.22 g, 1.2 mmol), and the mixture was stirred at room temperature for 12 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give methyl 2-[(3-{{[(tert-butoxycarbonyl)amino]methyl}-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-

20 isoquinolinyl]oxy]-2-methylpropanoate (0.31 g, 59.6%) as crystals.

Melting point 207-209°C.

Elemental analysis for C₃₀H₃₈N₂O₆ 0.25H₂O .

Calculated: C, 68.35; H, 7.36; N, 5.31.

25 Found: C, 68.39; H, 7.54; N, 5.31.

¹H-NMR(CDCl₃) δ: 0.99 (6H, d, J=6.6 Hz), 1.42 (9H, s), 1.51 (6H, s), 2.11-2.31 (1H, m), 3.53 (3H, s), 4.04 (2H, d, J=7.4 Hz), 4.18 (2H, d, J=5.4 Hz), 4.42 (1H, bs), 6.14 (1H, d, J=2.5 Hz), 6.94 (1H, dd, J=2.5, 8.8 Hz), 7.19-7.24 (2H, m), 7.46-7.57 (3H, m), 8.35 (1H, d, J=8.8 Hz).

(2) Methyl 2-[(3-{{[(tert-butoxycarbonyl)amino]methyl}-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]oxy]-2-methylpropanoate (0.16 g, 0.3 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The solution was stirred at room

temperature for 1 h. The reaction was concentrated under reduced pressure, and the precipitated crystals were recrystallized from ethyl acetate - diisopropyl ether to give methyl 2-{[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]oxy}-2-methylpropanoate hydrochloride(0.10 g, 71.4%) as crystals.

Melting point 236-237°C.

Elemental analysis for C₂₅H₃₁N₂O₄Cl 1.25H₂O

Calculated: C, 62.36; H, 7.01; N, 5.82.

Found: C, 62.32; H, 6.73; N, 5.58.

¹H-NMR(DMSO-d₆) δ: 0.91 (6H, d, J=6.6 Hz), 1.44 (6H, s), 1.99-2.18 (1H, m), 3.45 (3H, s), 3.84 (2H, s), 4.05 (2H, d, J=7.0 Hz), 5.99 (1H, d, J=2.4 Hz), 7.02 (1H, dd,

J=2.4, 8.8 Hz), 7.34-7.39 (2H, m), 7.55-7.62 (3H, m), 8.23 (1H, d, J=8.8 Hz), 8.57 (3H, bs).

Example 225

2-{[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]oxy}-2-methylpropanoic acid

hydrochloride

(1) To a solution of methyl 2-{[(tert-butoxycarbonyl)amino]methyl}-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]oxy]-2-methylpropanoate (0.37 g, 0.7 mmol) in tetrahydrofuran (10 ml) and

methanol (10 ml) was added 1N sodium hydroxide solution (2 ml). The mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried

over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting crystals were crystallized from ethyl acetate - diisopropyl ether to give 2-{[(tert-butoxycarbonyl)amino]methyl}-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-

isoquinolinyl]oxy]-2-methylpropanoic acid (0.32 g, 91.4%) as crystals.

Melting point 219-220°C.

Elemental analysis for C₂₉H₃₆N₂O₆

Calculated: C, 68.48; H, 7.13; N, 5.51.

Found: C, 68.48; H, 7.19; N, 5.28.

5 ¹H-NMR(CDCl₃) δ: 0.98 (6H, d, J=6.6 Hz), 1.42 (9H, s), 1.59 (6H, s), 2.16-2.32 (1H, m), 4.07 (2H, d, J=7.4 Hz), 4.19 (2H, d, J=5.2 Hz), 4.58 (1H, bs), 6.41 (1H, d, J=2.4 Hz), 6.97 (1H, dd, J=2.4, 8.8 Hz), 7.14-7.22 (2H, m), 7.41-7.56 (3H, m), 8.30 (1H, d, J=8.8 Hz).

10 (2) 2-[{3-{[(Tert-butoxycarbonyl)amino]methyl}-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]oxy]-2-methylpropanoic acid (0.13 g, 0.25 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The solution was

15 stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was crystallized from ethyl acetate to give 2-{{3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]oxy}-2-methylpropanoic acid

20 hydrochloride (0.10 g, 90.9%) as crystals.

Melting point 256-257°C.

Elemental analysis for C₂₄H₂₉N₂O₄Cl 0.5H₂O

Calculated: C, 63.50; H, 6.66; N, 6.17.

Found: C, 63.25; H, 6.66; N, 5.86.

25 ¹H-NMR(DMSO-d₆) δ: 0.91 (6H, d, J=6.6 Hz), 1.44 (6H, s), 1.99-2.14 (1H, m), 3.86 (2H, s), 4.03 (2H, d, J=6.9 Hz), 6.17 (1H, d, J=2.2 Hz), 7.01 (1H, dd, J=2.2, 8.7 Hz), 7.34-7.37 (2H, m), 7.49-7.58 (3H, m), 8.22 (1H, d, J=8.7 Hz), 8.49 (3H, bs).

30 Example 226

2-{{3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]oxy}-2-methylpropanamide hydrochloride

(1) A solution of 2-[{3-{[(tert-

35 butoxycarbonyl)amino]methyl}-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]oxy]-2-methylpropanoic acid

(0.20 g, 0.4 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.15 g, 0.8 mmol) and 1-hydroxybenzotriazole ammonium salt (0.12 g, 0.8 mmol) in N,N-dimethylformamide (10 ml) was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting crystals were recrystallized from ethyl acetate - diisopropyl ether to give tert-butyl [6-(2-amino-1,1-dimethyl-2-oxoethoxy)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.19 g, 95.0%) as crystals.

Melting point 219-220°C.
Elemental analysis for C₂₉H₃₇N₃O₅ 0.25H₂O
Calculated: C, 68.01; H, 7.38; N, 8.21.
Found: C, 68.04; H, 7.46; N, 7.97.
¹H-NMR(CDCl₃) δ: 1.00 (6H, d, J=6.4 Hz), 1.42 (9H, s), 1.46 (6H, s), 2.12-2.31 (1H, m), 4.05 (2H, d, J=7.2 Hz), 4.20 (2H, d, J=5.4 Hz), 4.45 (1H, bs), 5.36 (1H, bs), 6.34 (1H, bs), 6.39 (1H, d, J=2.6 Hz), 7.03 (1H, dd, J=2.6, 8.8 Hz), 7.20-7.25 (2H, m), 7.48-7.58 (3H, m), 8.39 (1H, d, J=8.8 Hz).

(2) Tert-butyl [6-(2-amino-1,1-dimethyl-2-oxoethoxy)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.15 g, 0.3 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The solution was stirred at room temperature for 1 h. The reaction was concentrated under reduced pressure, and the residue was crystallized from ethyl acetate to give 2-{[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]oxy}-2-methylpropanamide hydrochloride (0.12 g, 92.3%) crystals.
Melting point 182-184°C.

Elemental analysis for C₂₄H₃₀N₃O₃Cl AcOEt

Calculated: C, 63.21; H, 7.20; N, 7.90.

Found: C, 63.31; H, 7.47; N, 8.11.

¹H-NMR(DMSO-d₆) δ: 0.91 (6H, d, J=6.6 Hz), 1.38 (6H, s),
 5 1.99-2.18 (1H, m), 3.85 (2H, s), 4.04 (2H, d, J=6.8 Hz),
 6.27 (1H, d, J=2.2 Hz), 7.04 (1H, dd, J=2.2, 8.8 Hz),
 7.17 (1H, bs), 7.34-7.38 (2H, m), 7.44 (1H, bs), 7.54-
 7.61 (3H, m), 8.22 (1H, d, J=8.8 Hz), 8.55 (3H, bs).

Example 227

- 10 6-Acetyl-3-(aminomethyl)-4-butoxy-2-isobutyl-1(2H)-isoquinolinone hydrochloride
 (1) A solution of 4-butoxy-3-{{(tert-butoxycarbonyl)amino)methyl}-2-isobutyl-1-oxo-1,2-dihydro-6-isouquinolinecarboxylic acid (4.46 g, 10 mmol),
 15 N,O-dimethylhydroxyamine hydrochloride (1.17 g, 12 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (2.30 g, 12 mmol), 1-hydroxybenzotriazole (1.84 g, 12 mmol) and triethylamine (1.7 ml, 12 mmol) in N,N-dimethylformamide (10 ml) was stirred at room
 20 temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting crystals were recrystallized from ethyl acetate - diisopropyl ether to give tert-butyl (4-butoxy-2-isobutyl-6-{{methoxy(methyl)amino}carbonyl}-1-oxo-1,2-dihydro-3-isouquinolinyl)methylcarbamate (4.15 g, 84.9%) as crystals.

Melting point 142-143°C.

30 Elemental analysis for C₂₆H₃₉N₃O₆

Calculated: C, 63.78; H, 8.03; N, 8.58.

Found: C, 63.59; H, 8.10; N, 8.58.

¹H-NMR(CDCl₃) δ: 0.97 (6H, d, J=6.9 Hz), 1.02 (3H, t, J=7.0 Hz), 1.47 (9H, s), 1.48-1.62 (2H, m), 1.79-1.93
 35 (2H, m), 2.12-2.26 (1H, m), 3.41 (3H, s), 3.54 (3H, s), 3.88 (2H, t, J=6.5 Hz), 4.01 (2H, d, J=7.6 Hz), 4.53 (2H,

d, J=5.6 Hz), 4.74 (1H, bs), 7.74 (1H, dd, J=1.4, 8.6 Hz), 7.99 (1H, d, J=1.4 Hz), 8.46 (1H, d, J=8.6 Hz).
(2) To a solution of tert-butyl (4-butoxy-2-isobutyl-6-
isoquinolinyl)methylcarbamate (0.49 g, 1 mmol) in
tetrahydrofuran (10 ml) was added 1N methylmagnesium
bromide tetrahydrofuran solution (5 ml) at 0°C. The
mixture was stirred at 0°C for 1 h. The reaction mixture
was poured into water and extracted with ethyl acetate.
The extract was washed with brine, dried over anhydrous
magnesium sulfate and concentrated under reduced
pressure. The residue was purified by silica gel column
chromatography to give tert-butyl (6-acetyl-4-butoxy-2-
isobutyl-1-oxo-1,2-dihydro-3-
isoquinolinyl)methylcarbamate (0.37 g, 84.1%) as
crystals.
Melting point 161-162°C.
Elemental analysis for C₂₅H₃₆N₂O₅
Calculated: C, 67.54; H, 8.16; N, 6.30.
Found: C, 67.30; H, 8.14; N, 6.21.
¹H-NMR(CDCl₃) δ: 0.97 (6H, d, J=6.6 Hz), 1.06 (3H, t,
J=7.2 Hz), 1.47 (9H, s), 1.53-1.72 (2H, m), 1.82-1.97
(2H, m), 2.12-2.25 (1H, m), 2.71 (3H, s), 3.90 (2H, t,
J=6.5 Hz), 4.01 (2H, d, J=7.4 Hz), 4.54 (2H, d, J=5.6
Hz), 4.78 (1H, bs), 8.01 (1H, dd, J=2.0, 8.4 Hz), 8.28
(1H, d, J=2.0 Hz), 8.49 (1H, d, J=8.4 Hz).
(3) Tert-butyl (6-acetyl-4-butoxy-2-isobutyl-1-oxo-1,2-
dihydro-3-isoquinolinyl)methylcarbamate (0.13 g, 0.3
mmol) was dissolved in a solution of 4N hydrogen
chloride in ethyl acetate (5 ml). The solution was
stirred at room temperature for 1 h. The reaction was
concentrated under reduced pressure, and the
precipitated crystals were recrystallized from methanol
- diisopropyl ether to give 6-acetyl-3-(aminomethyl)-4-
butoxy-2-isobutyl-1(2H)-isoquinolinone hydrochloride
(0.10 g, 90.9%) as crystals.

Melting point 171.5-173°C.

Elemental analysis for C₂₀H₂₉N₂O₃Cl

Calculated: C, 63.06; H, 7.67; N, 7.35.

Found: C, 62.77; H, 7.77; N, 7.26.

5 ¹H-NMR(DMSO-d₆) δ: 0.89 (6H, d, J=6.6 Hz), 1.02 (3H, t, J=7.4 Hz), 1.52-1.70 (2H, m), 1.84-2.16 (3H, m), 2.72 (3H, s), 3.92-4.01 (4H, m), 4.20 (2H, s), 8.12 (1H, d, J=8.2 Hz), 8.26 (1H, s), 8.39 (1H, d, J=8.2 Hz), 8.70 (3H, bs).

10 The compounds of following Examples 228 to 252 were synthesized according to the method similar to that in Example 214 (2) from the N-Boc intermediates.

Example 228

(E)-3-[3-(Aminomethyl)-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenoic acid hydrochloride

Melting point 268-270°C.

Elemental analysis for C₂₃H₂₄N₂O₃Cl₂ 0.5H₂O

Calculated: C, 60.53; H, 5.52; N, 6.14.

20 Found: C, 60.49; H, 5.75; N, 5.81.

¹H-NMR(DMSO-d₆) δ: 0.92 (6H, d, J=6.6 Hz), 2.04-2.18 (1H, m), 3.86 (2H, s), 4.07 (2H, d, J=6.6 Hz), 6.52 (1H, d, J=15.9 Hz), 7.09 (1H, s), 7.44 (2H, d, J=8.1 Hz), 7.56 (1H, d, J=15.9 Hz), 7.64 (2H, d, J=8.1 Hz), 7.96 (1H, d, J=8.7 Hz), 8.33 (1H, d, J=8.7 Hz), 8.53 (3H, bs).

Example 229

Methyl 3-(aminomethyl)-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylate hydrochloride

Melting point 177-179°C.

30 Elemental analysis for C₂₂H₂₄N₂O₃Cl₂ 0.25H₂O

Calculated: C, 60.07; H, 5.61; N, 6.37.

Found: C, 60.00; H, 5.89; N, 6.24.

¹H-NMR(DMSO-d₆) δ: 0.93 (6H, d, J=6.6 Hz), 2.02-2.18 (1H, m), 3.82 (3H, s), 3.88 (2H, s), 4.08 (2H, d, J=7.0 Hz), 7.46 (2H, d, J=8.4 Hz), 7.61 (1H, d, J=1.6 Hz), 7.68 (2H, d, J=8.4 Hz), 8.08 (1H, dd, J=1.6, 8.4 Hz), 8.46 (1H, d,

J=8.4 Hz), 8.52 (3H, bs).

Example 230

3-(Aminomethyl)-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid hydrochloride

5 Melting point 263-265°C.

¹H-NMR(DMSO-d₆) δ: 0.93 (6H, d, J=6.6 Hz), 1.99-2.18 (1H, m), 3.88 (2H, s), 4.08 (2H, d, J=7.0 Hz), 7.46 (2H, d, J=8.4 Hz), 7.51 (1H, d, J=1.4 Hz), 7.67 (2H, d, J=8.4 Hz), 8.06 (1H, dd, J=1.4, 8.2 Hz), 8.44 (1H, d, J=8.2 Hz), 8.46 (3H, bs).

Example 231

3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinecarbothioamide hydrochloride

Melting point 257-259°C.

15 Elemental analysis for C₂₁H₂₄N₃OClS 0.5H₂O

Calculated: C, 61.37; H, 6.13; N, 10.22.

Found: C, 61.04; H, 5.99; N, 9.85.

¹H-NMR(DMSO-d₆) δ: 0.92 (6H, d, J=6.6 Hz), 1.99-2.18 (1H, m), 3.88 (2H, s), 4.06 (2H, d, J=7.2 Hz), 7.37-7.43 (3H, m), 7.56-7.59 (3H, m), 7.85 (1H, dd, J=1.5, 8.4 Hz),

20 8.32 (1H, d, J=8.4 Hz), 8.52 (3H, bs), 9.67 (1H, bs), 10.02 (1H, bs).

Example 232

3-(Aminomethyl)-6-(benzyloxy)-4-(4-chlorophenyl)-2-

25 isobutyl-1(2H)-isoquinolinone hydrochloride

Melting point 162-164°C.

Elemental analysis for C₂₇H₂₈N₂O₃Cl₂ 0.25H₂O

Calculated: C, 66.46; H, 5.89; N, 5.74.

Found: C, 66.26; H, 5.87; N, 5.49.

30 ¹H-NMR(DMSO-d₆) δ: 0.90 (6H, d, J=6.6 Hz), 1.98-2.13 (1H, m), 3.82 (2H, s), 4.03 (2H, d, J=7.0 Hz), 5.04 (2H, s), 6.26 (1H, d, J=2.6 Hz), 7.23-7.59 (8H, m), 7.61 (2H, d, J=8.4 Hz), 8.25 (1H, d, J=8.8 Hz), 8.52 (3H, bs).

Example 233

35 3-(Aminomethyl)-4-(4-chlorophenyl)-6-hydroxy-2-isobutyl-1(2H)-isoquinolinone hydrochloride

Melting point 247-249°C.

¹H-NMR(DMSO-d₆) δ: 0.90 (6H, d, J=7.0 Hz), 1.99-2.13 (1H, m), 3.82 (2H, s), 3.99 (2H, d, J=7.4 Hz), 6.19 (1H, d, J=2.2 Hz), 6.99 (1H, dd, J=2.2, 8.8 Hz), 7.40 (2H, d, J=8.4 Hz), 7.63 (2H, d, J=8.4 Hz), 8.16 (1H, d, J=8.8 Hz), 8.42 (3H, bs), 10.30 (1H, s).

Example 234

(E)-3-[3-(Aminomethyl)-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenoic acid

10 hydrochloride

Melting point 230-231°C.

Elemental analysis for C₂₅H₂₇N₂O₃Cl H₂O

Calculated: C, 64.78; H, 6.57; N, 6.30.

Found: C, 64.73; H, 6.63; N, 5.86.

15 ¹H-NMR(DMSO-d₆) δ: 0.92 (6H, d, J=6.6 Hz), 2.06-2.18 (1H, m), 2.45 (3H, s), 3.89 (2H, s), 4.07 (2H, d, J=6.6 Hz), 6.47 (1H, d, J=16.0 Hz), 7.05 (1H, d, J=1.2 Hz); 7.29 (2H, d, J=8.1 Hz), 7.40 (2H, d, J=8.1 Hz), 7.49 (1H, d, J=16.0 Hz), 7.94 (1H, dd, J=1.2, 8.1 Hz), 8.33 (1H, d, J=8.1 Hz), 8.50 (3H, bs).

Example 235

Methyl 3-(aminomethyl)-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-6-isoquinolinecarboxylate hydrochloride

Melting point 254-256°C.

25 Elemental analysis for C₂₃H₂₇N₂O₃Cl 0.25H₂O

Calculated: C, 65.86; H, 6.61; N, 6.68.

Found: C, 66.03; H, 6.67; N, 6.50.

¹H-NMR(DMSO-d₆) δ: 0.92 (6H, d, J=6.6 Hz), 2.06-2.16 (1H, m), 2.45 (3H, s), 3.81 (3H, s), 3.89 (2H, s), 4.10 (2H, d, J=6.9 Hz), 7.31 (2H, d, J=7.8 Hz), 7.41 (2H, d, J=7.8 Hz), 7.57 (1H, s), 8.06 (1H, d, J=8.3 Hz), 8.45 (1H, d, J=8.3 Hz), 8.57 (3H, bs).

Example 236

3-(Aminomethyl)-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid hydrochloride

Melting point 259-261°C.

Elemental analysis for $C_{22}H_{25}N_2O_3Cl$ 0.75H₂O

Calculated: C, 63.76; H, 6.45; N, 6.76.

Found: C, 63.66; H, 6.49; N, 6.50.

¹H-NMR(DMSO-d₆) δ: 0.92 (6H, d, J=6.6 Hz), 1.99-2.14 (1H, m), 2.45 (3H, s), 3.89 (2H, s), 4.09 (2H, d, J=7.4 Hz), 7.31 (2H, d, J=7.9 Hz), 7.42 (2H, d, J=7.9 Hz), 7.57 (1H, d, J=1.4 Hz), 8.05 (1H, dd, J=1.4, 8.4 Hz), 8.43 (1H, d, J=8.4 Hz), 8.53 (3H, bs).

Example 237

10 3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarbothioamide hydrochloride

Melting point 200-202°C.

¹H-NMR(DMSO-d₆) δ: 0.88 (6H, d, J=6.6 Hz), 1.00 (3H, t, J=7.3 Hz), 1.49-1.67 (2H, m), 1.79-2.08 (3H, m), 3.95-

15 4.01 (4H, m), 4.19 (2H, bs), 7.98 (1H, dd, J=1.5, 8.5 Hz), 8.20 (1H, d, J=1.5 Hz), 8.28 (1H, d, J=8.5 Hz), 8.51 (3H, bs), 9.87 (1H, bs), 10.20 (3H, bs).

Example 238

20 3-(Aminomethyl)-6-(benzyloxy)-2-isobutyl-4-(4-methylphenyl)-1(2H)-isoquinolinone hydrochloride

Melting point 244-246°C.

Elemental analysis for $C_{28}H_{31}N_2O_2Cl$

Calculated: C, 72.63; H, 6.75; N, 6.05..

Found: C, 72.31; H, 6.84; N, 5.93.

25 ¹H-NMR(DMSO-d₆) δ: 0.89 (6H, d, J=6.6 Hz), 1.98-2.18 (1H, m), 2.43 (3H, s), 3.84 (2H, s), 4.02 (2H, d, J=7.4 Hz), 5.01 (2H, s), 6.31 (1H, d, J=2.2 Hz), 7.18-7.38 (10H, m), 8.24 (1H, d, J=8.8 Hz), 8.45 (3H, bs).

Example 239

30 3-(Aminomethyl)-6-hydroxy-2-isobutyl-4-(4-methylphenyl)-1(2H)-isoquinolinone hydrochloride

Melting point 255-256°C.

¹H-NMR(DMSO-d₆) δ: 0.90 (6H, d, J=7.0 Hz), 1.99-2.13 (1H, m), 2.42 (3H, s), 3.83 (2H, s), 4.02 (2H, d, J=7.4 Hz),

35 6.23 (1H, d, J=2.4 Hz), 6.99 (1H, d, J=2.4, 8.6 Hz), 7.25 (2H, d, J=8.1 Hz), 7.37 (2H, d, J=8.1 Hz), 8.15 (1H,

d, J=8.6 Hz), 8.50 (3H, bs), 10.27 (1H, s).

Example 240

(E)-3-[3-(Aminomethyl)-4-(4-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenoic acid

5 hydrochloride

Melting point 255-256°C.

¹H-NMR(DMSO-d₆) δ: 0.93 (6H, d, J=6.6 Hz), 1.99-2.18 (1H, m), 3.87 (2H, s), 4.08 (2H, d, J=7.0 Hz), 6.50 (1H, d, J=16.2 Hz), 7.07 (1H, d, J=1.2 Hz), 7.36-7.48 (4H, m), 10 7.55 (1H, d, J=16.2 Hz), 7.95 (1H, dd, J=1.2, 8.0 Hz), 8.33 (1H, d, J=8.0 Hz), 8.59 (3H, bs).

Example 241

3-(Aminomethyl)-6-(benzyloxy)-4-(4-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone hydrochloride

15 Melting point 226-227°C.

Elemental analysis for C₂₇H₂₈N₂O₂ClF

Calculated: C, 69.44; H, 6.04; N, 6.00.

Found: C, 69.44; H, 5.89; N, 6.12.

¹H-NMR(DMSO-d₆) δ: 0.90 (6H, d, J=6.6 Hz), 1.99-2.14 (1H, m), 3.83 (2H, s), 4.04 (2H, d, J=7.4 Hz), 5.04 (2H, s), 6.26 (1H, d, J=2.6 Hz), 7.23-7.44 (10H, m), 8.25 (1H, d, J=8.8 Hz), 8.56 (3H, bs).

Example 242

3-(Aminomethyl)-4-(4-fluorophenyl)-6-hydroxy-2-isobutyl-1(2H)-isoquinolinone hydrochloride

Melting point 249-251°C.

Elemental analysis for C₂₀H₂₂N₂O₂ClF 1.5H₂O

Calculated: C, 59.48; H, 6.24; N, 6.94.

Found: C, 59.21; H, 5.99; N, 6.68.

30 ¹H-NMR(DMSO-d₆) δ: 0.91 (6H, d, J=6.6 Hz), 1.98-2.16 (1H, m), 3.82 (2H, d, J=7.0 Hz), 4.03 (2H, d, J=7.0 Hz), 6.19 (1H, d, J=2.2 Hz), 6.98 (1H, bs), 7.01 (1H, d, J=2.2, 8.8 Hz), 7.34-7.48 (4H, m), 8.16 (1H, d, J=8.8 Hz), 8.61 (3H, bs).

35 **Example 243**

Methyl 3-(aminomethyl)-4-(3-fluorophenyl)-2-isobutyl-1-

oxo-1,2-dihydro-6-isooquinolinecarboxylate hydrochloride
Melting point 177-179°C.

Elemental analysis for C₂₂H₂₄N₂O₃ClF 0.5H₂O

Calculated: C, 61.75; H, 5.89; N, 6.55.

5 Found: C, 61.55; H, 6.04; N, 6.34.

¹H-NMR(DMSO-d₆) δ: 0.93 (6H, d, J=6.6 Hz), 2.04-2.18 (1H, m), 3.81 (3H, s), 3.89 (2H, s), 3.89 (2H, d, J=7.8 Hz), 7.27-7.47 (3H, m), 7.51 (1H, d, J=1.3 Hz), 7.62-7.70 (1H, m), 8.08 (1H, dd, J=1.3, 8.4 Hz), 8.46 (1H, d, J=8.4 Hz), 10 8.59-8.67 (3H, m).

Example 244

3-(Aminomethyl)-4-(3-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isooquinolinecarboxylic acid hydrochloride

Melting point 252-254°C.

15 Elemental analysis for C₂₁H₂₂N₂O₃ClF 0.75H₂O

Calculated: C, 60.29; H, 5.66; N, 6.70.

Found: C, 60.29; H, 5.97; N, 6.53.

¹H-NMR(DMSO-d₆) δ: 0.93 (6H, d, J=6.6 Hz), 1.99-2.18 (1H, m), 3.89 (2H, bs), 4.04-4.17 (2H, m), 7.27-7.52 (4H, m), 20 7.60-7.71 (1H, m), 8.06 (1H, dd, J=1.2, 8.4 Hz), 8.44 (1H, d, J=8.4 Hz), 8.63 (3H, bs).

Example 245

3-(Aminomethyl)-6-(benzyloxy)-4-(3-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone hydrochloride

25 Melting point 178-180°C.

Elemental analysis for C₂₇H₂₈N₂O₂ClF 0.25H₂O

Calculated: C, 68.78; H, 6.09; N, 5.94.

Found: C, 68.57; H, 6.20; N, 5.84.

¹H-NMR(DMSO-d₆) δ: 0.90 (6H, d, J=6.6 Hz), 1.99-2.11 (1H, m), 3.77-3.90 (2H, m), 3.96-4.13 (2H, m), 5.04 (2H, s), 6.26 (1H, d, J=2.4 Hz), 7.16-7.43 (9H, m), 7.57-7.65 (1H, m), 8.25 (1H, d, J=8.7 Hz), 8.60 (3H, bs).

Example 246

3-(Aminomethyl)-4-(3-fluorophenyl)-6-hydroxy-2-isobutyl-

35 1(2H)-isoquinolinone hydrochloride

Melting point 226-227°C.

Elemental analysis for $C_{20}H_{22}N_2O_2ClF \cdot 1.5H_2O$

Calculated: C, 59.48; H, 6.24; N, 6.94.

Found: C, 59.28; H, 6.09; N, 6.85.

1H -NMR(DMSO-d₆) δ: 0.91 (6H, d, J=6.6 Hz), 1.98-2.12 (1H, m), 3.82 (2H, bs), 3.92-4.14 (2H, m), 6.20 (1H, d, J=2.4 Hz), 7.02 (1H, d, J=2.4, 8.6 Hz), 7.20-7.41 (3H, m), 7.56-7.67 (1H, m), 8.16 (1H, d, J=8.6 Hz), 8.60 (3H, bs).

Example 247

10 Methyl {[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]oxy}acetate hydrochloride

Melting point 228-229°C.

Elemental analysis for $C_{23}H_{27}N_2O_4Cl \cdot 0.25H_2O$

Calculated: C, 63.44; H, 6.37; N, 6.43.

15 Found: C, 63.53; H, 6.27; N, 6.30.

1H -NMR(DMSO-d₆) δ: 0.91 (6H, d, J=6.6 Hz), 1.99-2.18 (1H, m), 3.60 (3H, s), 3.86 (2H, s), 4.04 (2H, d, J=7.2 Hz), 4.71 (2H, s), 6.13 (1H, d, J=2.4 Hz), 7.20 (1H, dd, J=2.4, 8.8 Hz), 7.34-7.39 (2H, m), 7.54-7.60 (3H, m),

20 8.26 (1H, d, J=8.8 Hz), 8.47 (3H, bs).

Example 248

{[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]oxy}acetic acid hydrochloride

Melting point 255-257°C.

25 Elemental analysis for $C_{22}H_{25}N_2O_4Cl \cdot 0.5H_2O$

Calculated: C, 62.04; H, 6.15; N, 6.58.

Found: C, 62.15; H, 6.28; N, 6.36.

1H -NMR(DMSO-d₆) δ: 0.91 (6H, d, J=6.6 Hz), 1.99-2.18 (1H, m), 3.86 (2H, s), 4.05 (2H, d, J=7.6 Hz), 4.61 (2H, s),

30 6.20 (1H, d, J=2.2 Hz), 7.18 (1H, dd, J=2.2, 8.8 Hz), 7.35-7.40 (2H, m), 7.52-7.63 (3H, m), 8.26 (1H, d, J=8.8 Hz), 8.55 (3H, bs).

Example 249

Methyl 3-(aminomethyl)-4-(2-fluorophenyl)-2-isobutyl-1-

35 oxo-1,2-dihydro-6-isoquinolinecarboxylate hydrochloride

Melting point 243-245°C.

Elemental analysis for $C_{22}H_{24}N_2O_3ClF \cdot 1.0H_2O$

Calculated: C, 63.23; H, 6.27; N, 6.70.

Found: C, 63.08; H, 5.89; N, 6.46.

1H -NMR(DMSO-d₆) δ: 0.92 (3H, d, J=6.3 Hz), 0.94 (3H, d, J=5.7 Hz), 2.04-2.18 (1H, m), 3.77-3.80 (1H, m), 3.81 (3H, s), 3.97-4.05 (2H, m), 4.13-4.21 (1H, m), 7.44-7.58 (4H, m), 7.64-7.72 (1H, m), 8.10 (1H, dd, J=1.6, 8.7 Hz), 8.48 (1H, d, J=8.7 Hz), 8.66 (3H, bs).

Example 250

- 10 3-(Aminomethyl)-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid hydrochloride

Melting point 222-224°C.

Elemental analysis for $C_{21}H_{22}N_2O_3ClF \cdot 0.75H_2O$

Calculated: C, 60.29; H, 5.66; N, 6.70.

- 15 Found: C, 60.37; H, 5.76; N, 6.31.

1H -NMR(DMSO-d₆) δ: 0.92 (3H, d, J=6.6 Hz), 0.94 (3H, d, J=6.6 Hz), 2.05-2.17 (1H, m), 3.77-3.84 (1H, m), 3.95-4.22 (3H, m), 7.42-7.73 (5H, m), 8.08 (1H, dd, J=1.4, 8.2 Hz), 8.45 (1H, d, J=8.2 Hz), 8.66 (3H, bs).

20 Example 251

3-(Aminomethyl)-6-(benzyloxy)-4-(2-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone hydrochloride

Melting point 144-145°C.

Elemental analysis for $C_{27}H_{28}N_2O_2ClF \cdot 0.5H_2O$

- 25 Calculated: C, 68.13; H, 6.14; N, 5.89.

Found: C, 68.08; H, 6.43; N, 5.83.

1H -NMR(DMSO-d₆) δ: 0.89 (3H, d, J=6.6 Hz), 0.91 (3H, d, J=6.6 Hz), 1.99-2.16 (1H, m), 3.69-4.18 (4H, m), 5.04 (2H, s), 6.26 (1H, d, J=2.0 Hz), 7.22-7.47 (9H, m),

- 30 7.59-7.68 (1H, m), 8.26 (1H, d, J=8.8 Hz), 8.52 (3H, bs).

Example 252

3-(Aminomethyl)-4-(2-fluorophenyl)-6-hydroxy-2-isobutyl-1(2H)-isoquinolinone hydrochloride

Melting point 259-260°C.

- 35 Elemental analysis for $C_{20}H_{22}N_2O_2Cl$

Calculated: C, 63.74; H, 5.88; N, 7.43.

Found: C, 63.38; H, 5.71; N, 7.43.

¹H-NMR(DMSO-d₆) δ: 0.89 (3H, d, J=6.6 Hz), 0.91 (3H, d, J=6.6 Hz), 2.01-2.18 (1H, m), 3.68-4.16 (4H, m), 6.20 (1H, d, J=2.4 Hz), 7.02 (1H, dd, J=2.4, 8.6 Hz), 7.37-
5 7.67 (4H, m), 8.17 (1H, d, J=8.6 Hz), 8.55 (3H, bs), 10.37 (3H, bs).

Example 253

3-(Aminomethyl)-6-(benzyloxy)-2-isobutyl-4-(2-thienyl)-1(2H)-isoquinolinone hydrochloride

10 (1) A mixture of methyl 6-(benzyloxy)-2-isobutyl-1-oxo-4-trifluoromethanesulfonyloxy-1,2-dihydro-3-isoquinolinecarboxylate (10.26 g, 20 mmol), 2-thiopheneboronic acid (3.07 g, 24 mmol), sodium carbonate (5.30 g, 50 mmol), toluene (50 ml), methanol
15 (10 ml) and water (10 ml) was stirred at room temperature for 30 min under an argon atmosphere. To the resulting mixture was added tetrakis(triphenylphosphine)palladium (1.16 g, 1 mmol), the mixture was refluxed under heating for 10 h under an
20 argon atmosphere. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography
25 to give methyl 6-(benzyloxy)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-3-isoquinolinecarboxylate (2.11 g, 23.6%) as crystals.

Melting point 143-144°C.

Elemental analysis for C₂₆H₂₅NO₄S

30 Calculated: C, 69.78; H, 5.63; N, 3.13.

Found: C, 69.77; H, 5.76; N, 3.15.

¹H-NMR(CDCl₃) δ: 0.92 (6H, d, J=7.0 Hz), 2.05-2.21 (1H, m), 3.59 (3H, s), 3.92 (2H, d, J=7.8 Hz), 5.02 (2H, s), 6.85 (1H, d, J=2.6 Hz), 6.98 (1H, dd, J=1.2, 3.4 Hz),
35 7.10 (1H, dd, J=3.4, 5.1 Hz), 7.17 (1H, dd, J=2.4, 9.1 Hz), 7.29-7.42 (5H, m), 7.46 (1H, dd, J=1.2, 5.1 Hz),

8.39 (1H, d, J=9.1 Hz).

(2) To a suspension of methyl 6-(benzyloxy)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-3-

isoquinolinecarboxylate (2.01 g, 4.5 mmol) in methanol

- 5 (30 ml) was added a solution of lithium hydroxide monohydrate (0.57 g, 13.5 mmol) in water (10 ml). The resulting mixture was refluxed under heating for 48 h. The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting crystals were recrystallized from ethyl acetate - n-hexane to give 6-(benzyloxy)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-3-isoquinolinecarboxylic acid (1.71 g, 87.7%) as crystals.

Melting point 171-172°C.

Elemental analysis for C₂₅H₂₃NO₄S 0.3H₂O:

Calculated: C, 68.41; H, 5.42; N, 3.19.

20 Found: C, 68.51; H, 5.84; N, 2.93.

¹H-NMR(CDCl₃) δ: 0.87 (6H, d, J=6.6 Hz), 2.13-2.26 (1H, m), 3.89 (2H, d, J=7.4 Hz), 5.00 (2H, s), 6.79 (1H, d, J=1.8 Hz), 7.08-7.13 (3H, m), 7.27-7.45 (5H, m), 7.46-7.48 (1H, m), 8.26 (1H, dd, J=1.4, 9.0 Hz).

- 25 (3) To a solution of 6-(benzyloxy)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-3-isoquinolinecarboxylic acid (1.52 g, 3.5 mmol) in tetrahydrofuran (20 ml) were added oxalyl chloride (0.37 ml, 4.2 mmol) and N,N-dimethylformamide (2drops). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (10 ml). The solution was added dropwise to a suspension of sodium tetrahydroborate (0.47 g, 12.3 mmol) in 1,2-dimethoxyethane (20 ml) at 0°C, and the mixture was stirred at 0°C for 1 h. The reaction mixture was poured

into 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 6-(benzyloxy)-3-(hydroxymethyl)-2-isobutyl-4-(2-thienyl)-1(2H)-isoquinolinone (1.36 g, 92.5%) as crystals.

Elemental analysis for C₂₅H₂₅NO₃S
Calculated: C, 71.57; H, 6.01; N, 3.34.
Found: C, 71.32; H, 6.08; N, 3.25.

¹H-NMR(CDCl₃) δ: 0.96 (6H, d, J=7.0 Hz), 2.11-2.35 (1H, m), 4.18 (2H, d, J=7.4 Hz), 4.53 (2H, d, J=6.2 Hz), 4.94 (2H, s), 6.55 (1H, d, J=2.2 Hz), 7.00-7.05 (2H, m), 7.18 (1H, dd, J=3.5, 5.2 Hz), 7.23-7.38 (5H, m), 7.48 (1H, dd, J=1.0, 5.2 Hz), 8.30 (1H, d, J=9.0 Hz).

(4) To a suspension of 6-(benzyloxy)-3-(hydroxymethyl)-2-isobutyl-4-(2-thienyl)-1(2H)-isoquinolinone (1.26 g, 3 mmol) in toluene (20 ml) was added thionyl chloride (0.44 ml, 6 mmol). The resulting mixture was refluxed for 2 h. The reaction mixture was added to a saturated sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 6-(benzyloxy)-3-(chloromethyl)-2-isobutyl-4-(2-thienyl)-1(2H)-isoquinolinone (1.30 g, 100%) as an oil.

¹H-NMR(CDCl₃) δ: 1.00 (6H, d, J=6.6 Hz), 2.12-2.31 (1H, m), 4.14 (2H, bs), 4.48 (2H, s), 4.99 (2H, s), 6.61 (1H, d, J=2.6 Hz), 7.05 (1H, dd, J=1.6, 3.5 Hz), 7.11-7.38 (7H, m), 7.51 (1H, dd, J=1.6, 5.1 Hz), 8.38 (1H, d, J=8.8 Hz).

(5) A solution of 6-(benzyloxy)-3-(chloromethyl)-2-isobutyl-4-(2-thienyl)-1(2H)-isoquinolinone (1.31 g, 3 mmol) and potassium phthalimide (0.83 g, 4.5 mmol) in N,N-dimethylformamide (20 ml) was stirred at room temperature for 3 h. The reaction mixture was poured

into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography 5 to give 2-{{[6-(benzyloxy)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-3-isoquinolinyl]methyl}-1H-isoindole-1,3(2H)-dione (1.42 g, 86.6%) as an amorphous solid.

¹H-NMR(CDCl₃) δ: 0.98 (6H, d, J=6.6 Hz), 2.12-2.25 (1H, m), 4.02 (1H, d, J=6.6 Hz), 4.87 (2H, d, J=3.2 Hz), 4.97 (2H, s), 6.55 (1H, d, J=2.2 Hz), 7.01 (1H, dd, J=1.3, 3.5 Hz), 7.08-7.14 (2H, m), 7.28-7.39 (5H, m), 7.43 (1H, dd, J=1.3, 5.3 Hz), 7.68-7.80 (4H, m), 8.36 (1H, d, J=9.2 Hz).

15 (6) To a suspension of 2-{{[6-(benzyloxy)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-3-isoquinolinyl]methyl}-1H-isoindole-1,3(2H)-dione (1.37 g, 2.5 mmol) in ethanol (20 ml) was added hydrazine monohydrate (0.36 ml, 7.5 mmol). The mixture was refluxed for 1 h. The reaction 20 mixture was poured into a saturated sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in 25 tetrahydrofuran (20 ml), and then di-t-butyl dicarbonate (0.69 ml, 3 mmol) was added thereto. The resulting mixture was refluxed for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous 30 magnesium sulfate and concentrated under reduced pressure. The resulting crystals were recrystallized from ethyl acetate - diisopropyl ether to give tert-butyl [6-(benzyloxy)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-3-isoquinolinyl]methylcarbamate (1.19 g, 92.2%) 35 as crystals.

Melting point 176-177°C.

Elemental analysis for C₃₀H₃₄N₂O₄S

Calculated: C, 69.47; H, 6.61; N, 5.40.

Found: C, 69.44; H, 6.68; N, 5.36.

- ¹H-NMR(CDCl₃) δ: 0.98 (6H, d, J=7.0 Hz), 1.43 (9H, s),
5 2.14-2.28 (1H, m), 4.05 (2H, bs), 4.30 (2H, d, J=5.0 Hz),
4.56 (1H, bs), 4.98 (2H, s), 6.55 (1H, d, J=2.6 Hz),
6.94 (1H, dd, J=1.2, 3.5 Hz), 7.10 (1H, dd, J=2.6, 8.8
Hz), 7.17 (1H, dd, J=3.5, 5.4 Hz), 7.26-7.39 (5H, m),
7.48 (1H, dd, J=1.2, 5.4 Hz), 8.35 (1H, d, J=8.8 Hz).
10 (7) Tert-butyl [6-(benzyloxy)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-3-isoquinolinyl]methylcarbamate
(0.15 g, 0.3 mmol) was dissolved in a solution of 4N
hydrogen chloride in ethyl acetate (5 ml). The solution
was stirred at room temperature for 1 h. The reaction
15 mixture was concentrated under reduced pressure, and the
precipitated crystals were recrystallized from ethyl
acetate - diisopropyl ether to give 3-(aminomethyl)-6-
(benzyloxy)-2-isobutyl-4-(2-thienyl)-1(2H)-
isoquinolinone hydrochloride (0.11 g, 84.6%) as crystals.
20 Melting point 139-141°C.

Elemental analysis for C₂₅H₂₇N₂O₂ClS 0.5H₂O.

Calculated: C, 64.71; H, 6.08; N, 6.04.

Found: C, 65.01; H, 6.18; N, 5.74.

- ¹H-NMR(DMSO-d₆) δ: 0.89 (6H, d, J=6.6 Hz), 1.99-2.09 (1H,
25 m), 3.98 (2H, bs), 4.08 (2H, bs), 5.06 (2H, bs), 6.49 (1H,
d, J=2.2 Hz), 7.20-7.41 (8H, m), 7.85 (1H, dd, J=1.1,
5.1 Hz), 8.23 (1H, d, J=9.0 Hz), 8.59 (3H, bs).

Example 254

- 3-(Aminomethyl)-6-hydroxy-2-isobutyl-4-(2-thienyl)-
30 1(2H)-isoquinolinone hydrochloride
(1) A suspension of tert-butyl [6-(benzyloxy)-2-
isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-3-
isoquinolinyl]methylcarbamate (1.04 g, 2 mmol) and 5%
palladium carbon (1.0 g) in ethanol (10 ml) and
35 tetrahydrofuran (10 ml) was stirred under a hydrogen
atmosphere at room temperature for 2 h. The catalyst was

filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [6-hydroxy-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.82 g, 96.5%) as crystals.

Melting point 216-217°C.

Elemental analysis for C₂₃H₂₈N₂O₄S

Calculated: C, 64.46; H, 6.59; N, 6.54.

Found: C, 64.38; H, 6.60; N, 6.33.

¹H-NMR(CDCl₃) δ: 0.97 (6H, d, J=6.6 Hz), 1.43 (9H, s), 2.13-2.25 (1H, m), 4.04 (2H, bs), 4.30 (2H, d, J=5.2 Hz), 4.57 (1H, bs), 6.53 (1H, d, J=2.4 Hz), 6.97 (1H, d, J=2.8 Hz), 7.03 (1H, dd, J=2.4, 8.8 Hz); 7.13 (1H, dd, J=2.8, 5.6 Hz), 7.40 (1H, bs), 7.42 (1H, d, J=5.6 Hz), 8.28 (1H, d, J=8.8 Hz).

(2) Tert-butyl [6-hydroxy-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-3-isoquinolinyl]methylcarbamate.

(0.15 g, 0.35 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate solution (5 ml). The solution was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the residue was crystallized from ethyl acetate - diisopropyl ether to give 3-(aminomethyl)-6-hydroxy-2-

isobutyl-4-(2-thienyl)-1(2H)-isoquinolinone hydrochloride (0.10 g, 83.3%) as crystals.

Melting point 249-251°C.

Elemental analysis for C₁₈H₂₁N₂O₂ClS H₂O

Calculated: C, 56.46; H, 6.05; N, 7.32.

Found: C, 56.54; H, 6.35; N, 7.06.

¹H-NMR(DMSO-d₆) δ: 0.90 (6H, d, J=6.6 Hz), 1.99-2.12 (1H, m), 3.98 (2H, bs), 4.08 (2H, bs), 6.41 (1H, d, J=2.3 Hz), 7.03 (1H, dd, J=2.3, 8.6 Hz), 7.06 (1H, bs), 7.26-7.29 (2H, m), 7.82 (1H, dd, J=2.8, 3.8 Hz), 8.14 (1H, d, J=8.6 Hz), 8.67 (3H, bs).

Example 255

2-{{[3-(Aminomethyl)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-6-isooquinolinyl]oxy}acetamide hydrochloride

- (1) A solution of tert-butyl [6-hydroxy-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-3-isooquinolinyl]methylcarbamate (0.43 g, 1 mmol), and 2-iodoacetamide (0.37 g, 2 mmol) and 1,8-diazabicyclo[5.4.0]-7-undecene (0.30 ml, 2 mmol) in N,N-dimethylacetamide (10 ml) was stirred at 80°C for 10 h.
- The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [6-(2-amino-2-oxoethoxy)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-3-isooquinolinyl]methylcarbamate (0.19 g, 39.6%) as crystals.

Melting point 219-221°C.

Elemental analysis for C₂₅H₃₁N₃O₅S 0.25H₂O

Calculated: C, 61.27; H, 6.48; N, 8.57.

Found: C, 61.02; H, 6.38; N, 8.37.

¹H-NMR(CDCl₃) δ: 0.99 (6H, d, J=6.6 Hz), 1.44 (9H, s), 2.16-2.26 (1H, m), 4.07 (2H, bs), 4.31 (2H, d, J=6.0 Hz), 4.39 (2H, s), 4.61 (1H, bs), 5.72 (1H, bs), 6.50 (1H, d, J=2.5 Hz), 6.51 (1H, bs), 7.01 (1H, dd, J=1.2, 3.6 Hz), 7.06 (1H, dd, J=2.5, 8.9 Hz), 7.20 (1H, dd, J=3.6, 5.4 Hz), 7.51 (1H, dd, J=1.2, 5.4 Hz), 8.40 (1H, d, J=8.9 Hz).

(2) Tert-butyl [6-(2-amino-2-oxoethoxy)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-3-isooquinolinyl]methylcarbamate (0.14 g, 0.3 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The solution was stirred at room temperature for 2 h. The reaction was concentrated under reduced pressure to give 2-{{[3-(aminomethyl)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-6-

isoquinolinyl]oxy}acetamide hydrochloride (0.11 g, 91.7%) as an amorphous solid.

¹H-NMR(DMSO-d₆) δ: 0.90 (6H, d, J=6.6 Hz), 1.99-2.14 (1H, m), 3.98-4.09 (4H, m), 4.41 (2H, s), 6.50 (1H, d, J=2.6 Hz), 7.21 (1H, dd, J=2.6, 9.0 Hz), 7.26-7.30 (2H, m), 7.35 (1H, bs), 7.60 (1H, bs), 7.83 (1H, dd, J=2.6, 4.0 Hz), 8.26 (1H, d, J=9.0 Hz), 8.63 (3H, s).

Example 256

Methyl 3-(aminomethyl)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-6-isoquinolinecarboxylate hydrochloride
(1) To a solution of tert-butyl [6-hydroxy-2-isobutyl-1-

oxo-4-(2-thienyl)-1,2-dihydro-3-isoquinolinyl]methylcarbamate (1.07 g, 2.5 mmol) in N,N-dimethylformamide (10 ml) was added sodium hydride (0.12 g, 3 mmol)(60% in oil) at 0°C, and then the mixture was stirred at 0°C for 30 min. To the mixture was added N-phenyltrifluoromethanesulfonimide (1.07 g, 3 mmol), and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give

tert-butyl [2-isobutyl-1-oxo-4-(2-thienyl)-6-trifluoromethanesulfonyloxy-1,2-dihydro-3-

isoquinolinyl]methylcarbamate (1.40 g, 100%) as an oil.

¹H-NMR(CDCl₃) δ: 0.99 (6H, d, J=6.6 Hz), 1.44 (9H, s), 2.15-2.27 (1H, m), 4.11 (2H, bs), 4.35 (2H, d, J=5.2 Hz), 4.58 (1H, bs), 7.00-7.06 (2H, m), 7.20-7.45 (2H, m), 7.53 (1H, dd, J=1.2, 5.3 Hz), 8.52 (1H, d, J=8.4 Hz).

(2) A mixture of tert-butyl [2-isobutyl-1-oxo-4-(2-thienyl)-6-trifluoromethanesulfonyloxy-1,2-dihydro-3-isoquinolinyl]methylcarbamate (1.40 g, 2.5 mmol), 1,1'-bis(diphenylphosphino)ferrocene (66 mg, 0.12 mmol), triethylamine (0.39 ml, 2.8 mmol) and palladium acetate (27 mg, 0.12 mmol) in tetrahydrofuran (20 ml) and

methanol (20 ml) was stirred at 100°C under a carbon monoxide atmosphere at 5 atm for 3 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over 5 anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give methyl 3-[(tert-butoxycarbonyl)amino]methyl}-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-6-isoquinolinecarboxylate (1.02 g, 10 87.2%) as crystals.

Melting point 170-171°C.

Elemental analysis for C₂₅H₃₀N₂O₅S

Calculated: C, 63.81; H, 6.43; N, 5.95.

Found: C, 63.68; H, 6.68; N, 5.68.

15 ¹H-NMR(CDCl₃) δ: 1.01 (6H, d, J=7.0 Hz), 1.44 (9H, s), 2.17-2.31 (1H, m), 3.88 (3H, s), 4.10 (2H, d, J=7.4 Hz), 4.34 (2H, d, J=5.8 Hz), 4.64 (1H, bs), 7.05 (1H, dd, J=1.1, 3.4 Hz), 7.21 (1H, dd, J=3.4, 5.2 Hz), 7.52 (1H, dd, J=1.1, 5.2 Hz), 7.82 (1H, d, J=1.3 Hz), 8.04 (1H, dd, 20 J=1.3, 8.4 Hz), 8.48 (1H, dd, J=0.8, 8.4 Hz).

(3) Methyl 3-[(tert-butoxycarbonyl)amino]methyl}-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-6-isoquinolinecarboxylate (0.14 g, 0.3 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate 25 (5 ml). The solution was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the residue was crystallized from ethyl acetate - diisopropyl ether to give methyl 3-(aminomethyl)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-6-isoquinolinecarboxylate hydrochloride (0.11 g, 30 91.7%) as crystals.

Melting point 227-229°C.

Elemental analysis for C₂₀H₂₃N₂O₃ClS 0.25H₂O

Calculated: C, 58.39; H, 5.76; N, 6.81.

35 Found: C, 58.28; H, 6.09; N, 6.41.

¹H-NMR(DMSO-d₆) δ: 0.92 (6H, d, J=6.6 Hz), 1.99-2.18 (1H,

m), 3.35 (2H, s), 3.84 (3H, s), 4.03 (2H, bs), 7.29-7.33 (2H, m), 7.72 (1H, d, J=1.4 Hz), 7.88 (1H, dd, J=2.6, 4.0 Hz), 8.08 (1H, dd, J=1.4, 8.4 Hz), 8.44 (1H, d, J=8.4 Hz), 8.69 (3H, bs).

5 Example 257

3-(Aminomethyl)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-6-isoquinolinecarboxylic acid hydrochloride

(1) To a solution of methyl 3-{{(tert-butoxycarbonyl)amino}methyl}-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-6-isoquinolinecarboxylate (0.85 g, 1.8 mmol) in tetrahydrofuran (10 ml) and methanol (10 ml) was added 1N sodium hydroxide solution (4 ml). The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting crystals were recrystallized from tetrahydrofuran - diisopropyl ether to give 3-{{(tert-butoxycarbonyl)amino}methyl}-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-6-isoquinolinecarboxylic acid (0.79 g, 96.3%) as crystals. Melting point 224-226°C.

Elemental analysis for C₂₄H₂₈N₂O₅S

25 Calculated: C, 63.14; H, 6.18; N, 6.14.

Found: C, 63.00; H, 6.04; N, 5.94.

¹H-NMR(CDCl₃) δ: 0.99 (6H, d, J=6.6 Hz), 1.49 (9H, s), 2.12-2.26 (1H, m), 4.05 (2H, d, J=6.4 Hz), 4.30 (2H, d, J=4.4 Hz), 5.61 (1H, bs), 7.09 (1H, d, J=3.5 Hz), 7.21 (1H, dd, J=3.5, 5.2 Hz), 7.53 (1H, dd, J=0.9, 5.2 Hz), 7.65 (1H, s), 7.91 (1H, d, J=8.6 Hz), 8.36 (1H, d, J=8.6 Hz).

(2) 3-{{(Tert-butoxycarbonyl)amino}methyl}-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-6-isoquinolinecarboxylic acid (0.14 g, 0.3 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The

solution was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was crystallized from ethyl acetate - diisopropyl ether to give 3-(aminomethyl)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-6-isoquinolinecarboxylic acid hydrochloride (0.10 g, 90.9%) as crystals.

5 Melting point 208-210°C.

Elemental analysis for C₁₉H₂₁N₂O₃ClS H₂O

Calculated: C, 55.54; H, 5.64; N, 6.82.

10 Found: C, 55.37; H, 5.74; N, 6.60.

¹H-NMR(DMSO-d₆) δ: 0.92 (6H, d, J=6.8 Hz), 1.99-2.19 (1H, m), 3.33 (2H, s), 4.04 (2H, s), 7.28-7.32 (2H, m), 7.72 (1H, d, J=1.4 Hz), 7.86-7.89 (1H, m), 8.06 (1H, dd, J=1.7, 8.2 Hz), 8.41 (1H, d, J=8.2 Hz), 8.60 (3H, bs).

15 Example 258

3-(Aminomethyl)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-6-isoquinolinecarboxamide hydrochloride

(1) A solution of 3-{[(tert-

butoxycarbonyl)amino]methyl}-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-6-isoquinolinecarboxylic acid (0.59 g, 1.3 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.50 g, 2.6 mmol) and 1-hydroxybenzotriazole ammonium salt (0.40 g, 2.6 mmol) in N,N-dimethylformamide (10 ml) was

25 stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting crystals were

30 recrystallized from tetrahydrofuran - diisopropyl ether to give tert-butyl [6-(aminocarbonyl)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.56 g, 94.9%) as crystals.

35 Melting point 248-250°C.

Elemental analysis for C₂₄H₂₉N₃O₄S

Calculated: C, 63.27; H, 6.42; N, 9.22.

Found: C, 62.99; H, 6.62; N, 9.00.

¹H-NMR(CDCl₃) δ: 0.99 (6H, d, J=7.0 Hz), 1.46 (9H, s), 2.14-2.27 (1H, m), 4.08 (2H, d, J=7.4 Hz), 4.31 (2H, d, 5 J=5.4 Hz), 5.01 (1H, bs), 6.23 (2H, bs), 7.06 (1H, d, J=2.6 Hz), 7.17 (1H, dd, J=2.6, 5.2 Hz), 7.48 (1H, d, J=5.2 Hz), 7.52 (1H, d, J=1.7 Hz), 7.73 (1H, dd, J=1.7, 8.4 Hz), 8.38 (1H, d, J=8.4 Hz).

(2) Tert-butyl [6-(aminocarbonyl)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.23 g, 0.5 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The solution was stirred at room temperature for 1 h. The reaction was concentrated under reduced pressure, and the 15 precipitated crystals were crystallized from methanol - diethyl ether to give 3-(aminomethyl)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-6-isoquinolinecarboxamide hydrochloride (0.18 g, 94.7%) as crystals.

Melting point 246-248°C.

20 Elemental analysis for C₁₉H₂₂N₃O₃ClS 0.75H₂O

Calculated: C, 56.29; H, 5.84; N, 10.36.

Found: C, 56.19; H, 5.97; N, 10.22.

¹H-NMR(DMSO-d₆) δ: 0.92 (6H, d, J=6.6 Hz), 2.02-2.18 (1H, m), 3.43 (2H, bs), 4.02 (2H, bs), 7.29-7.33 (2H, m), 25 7.61-7.63 (2H, m), 7.84-7.87 (1H, m), 8.01 (1H, dd, J=1.5, 8.4 Hz), 8.19 (1H, bs), 8.35 (1H, d, J=8.4 Hz), 8.60 (3H, bs).

Example 259

3-(Aminomethyl)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-6-isoquinolinecarbonitrile hydrochloride
30 (1) A solution of tert-butyl [6-(aminocarbonyl)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.23 g, 0.5 mmol) and cyanuric chloride (0.28 g, 1.5 mmol) in N,N-dimethylformamide (10 mmol) was stirred at 0°C for 1 h. The reaction mixture was poured into water and extracted

with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [6-
5 cyano-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.20 g, 95.2%) as crystals.

Melting point 189-190°C.

Elemental analysis for C₂₄H₂₇N₃O₃S

10 Calculated: C, 65.88; H, 6.22; N, 9.60.

Found: C, 65.96; H, 6.14; N, 9.51.

¹H-NMR(CDCl₃) δ: 1.00 (6H, d, J=7.0 Hz), 1.44 (9H, s), 2.14-2.31 (1H, m), 4.10 (2H, bs), 4.36 (2H, bs), 4.57 (1H, bs), 7.03 (1H, dd, J=1.2, 3.6 Hz), 7.23 (1H, dd,
15 J=3.6, 5.1 Hz), 7.46 (1H, d, J=1.5 Hz), 7.55 (1H, dd, J=1.2, 5.1 Hz), 7.65 (1H, dd, J=1.5, 8.2 Hz), 8.52 (1H, d, J=8.2 Hz).

(2) Tert-butyl [6-cyano-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.17 g, 0.4 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The solution was stirred at room temperature for 1 h. The reaction was concentrated under reduced pressure, and the residue was crystallized from ethyl acetate - diisopropyl ether to give 3-(aminomethyl)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-6-isoquinolinecarbonitrile hydrochloride (0.14 g, 93.3%) as crystals.

Melting point 202-203°C.

¹H-NMR(DMSO-d₆) δ: 0.92 (6H, d, J=6.6 Hz), 2.06-2.16 (1H, m), 3.98-4.09 (4H, m), 7.29-7.33 (2H, m), 7.41 (1H, s), 7.87-7.91 (1H, m), 7.98 (1H, dd, J=1.1, 8.4 Hz), 8.46 (1H, d, J=8.4 Hz), 8.69 (3H, bs).

Example 260

3-(Aminomethyl)-4-butoxy-2-isobutyl-6-(2-pyridyl)-1(2H)-isoquinolinone dihydrochloride

(1) A solution of tert-butyl (6-bromo-4-butoxy-2-

isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.48 g, 1 mmol), tri-n-butyl(2-pyridyl)tin (0.37 g, 1 mmol) and tetrakis(triphenylphosphine)palladium (58 mg, 0.05 mmol) in N,N-dimethylformamide (10 ml) was stirred at 100°C for 10 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [4-butoxy-2-isobutyl-1-oxo-6-(2-pyridyl)-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.36 g, 75.0%) as crystals.

Melting point 123-124°C.

Elemental analysis for $C_{28}H_{37}N_3O_4$

Calculated: C, 70.12; H, 7.78; N, 8.76.

Found: C, 69.91; H, 8.07; N, 8.71.

1H -NMR(CDCl₃) δ: 0.98 (6H, d, J=6.6 Hz), 1.05 (3H, t, J=7.3 Hz), 1.47 (9H, s), 1.53-1.72 (2H, m), 1.84-1.97

(2H, m), 2.05-2.27 (1H, m), 3.94 (2H, t, J=6.4 Hz), 4.01 (2H, d, J=7.8 Hz), 4.55 (2H, d, J=5.4 Hz), 4.82 (1H, bs), 7.28-7.37 (1H, m), 7.77-7.85 (2H, m), 8.13 (1H, dd, J=1.8, 8.4 Hz), 8.32 (1H, d, J=1.8 Hz), 8.50 (1H, d, J=8.4 Hz), 8.74-8.78 (1H, m).

(2) Tert-butyl [4-butoxy-2-isobutyl-1-oxo-6-(2-pyridyl)-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.31 g, 0.65 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The solution was stirred at room temperature for 2 h. The reaction was concentrated under reduced pressure to give 3-(aminomethyl)-4-butoxy-2-isobutyl-6-(2-pyridyl)-1(2H)-isoquinolinone dihydrochloride (0.27 g, 93.1%) as an amorphous solid.

Elemental analysis for $C_{23}H_{31}N_3O_2Cl_2 \cdot H_2O$

Calculated: C, 58.72; H, 7.07; N, 8.93.

Found: C, 59.20; H, 7.46; N, 8.91.

¹H-NMR(DMSO-d₆) δ: 0.91 (6H, d, J=6.3 Hz), 1.01 (3H, t, J=7.2 Hz), 1.56-1.64 (2H, m), 1.87-1.95 (2H, m), 1.99-2.18 (1H, m), 4.02-4.06 (4H, m), 4.23 (2H, bs), 7.73 (1H, bs), 8.27-8.28 (3H, m), 8.42-8.44 (2H, m), 8.46 (4H, bs).

5 Example 261

3-(Aminomethyl)-4-butoxy-2-isobutyl-6-(2-thienyl)-1(2H)-isoquinolinone hydrochloride

(1) A solution of tert-butyl (6-bromo-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-

10 isoquinolinyl)methylcarbamate (0.48 g, 1 mmol), tri-n-butyl(2-thienyl)tin (0.32 ml, 1 mmol) and tetrakis(triphenylphosphine)palladium (58 mg, 0.05 mmol) in tetrahydrofuran (20 ml) was refluxed for 12 h. The reaction mixture was poured into water and extracted

15 with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [4-butoxy-2-isobutyl-1-oxo-6-(2-thienyl)-1,2-dihydro-3-

20 isoquinolinyl)methylcarbamate (0.22 g, 45.8%) as crystals.

Melting point 130-131°C.

Elemental analysis for C₂₇H₃₆N₂O₄S

Calculated: C, 66.91; H, 7.49; N, 5.78.

25 Found: C, 66.85; H, 7.56; N, 5.70.

¹H-NMR(CDCl₃) δ: 0.97 (6H, d, J=6.6 Hz), 1.06 (3H, t, J=7.3 Hz), 1.47 (9H, s), 1.55-1.73 (2H, m), 1.83-1.97 (2H, m), 2.05-2.25 (1H, m), 3.91 (2H, t, J=6.4 Hz), 3.99 (2H, d, J=7.4 Hz), 4.53 (2H, d, J=5.6 Hz), 4.75 (1H, bs), 7.15 (1H, dd, J=3.6, 5.2 Hz), 7.39 (1H, dd, J=1.1, 5.2 Hz), 7.48 (1H, dd, J=1.1, 3.6 Hz), 7.75 (1H, dd, J=1.6, 8.4 Hz), 7.90 (1H, d, J=1.6 Hz), 8.40 (1H, d, J=8.4 Hz).

(2) Tert-butyl [4-butoxy-2-isobutyl-1-oxo-6-(2-thienyl)-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.15 g, 0.3

35 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The solution was

stirred at room temperature for 2 h. The reaction was concentrated under reduced pressure, and the resulting crystals were recrystallized from methanol - diisopropyl ether to give 3-(aminomethyl)-4-butoxy-2-isobutyl-6-(2-thienyl)-1(2H)-isoquinolinone hydrochloride (0.11 g, 91.7%) as crystals.

Melting point 167-170°C.

¹H-NMR(DMSO-d₆) δ: 0.89 (6H, d, J=6.6 Hz), 1.03 (3H, t, J=7.3 Hz), 1.56-1.73 (2H, m), 1.82-2.11 (3H, m), 3.95-4.01 (4H, m), 4.20 (2H, s), 7.24 (1H, dd, J=3.7, 5.1 Hz), 7.72-7.76 (2H, m), 7.90 (1H, d, J=1.6 Hz), 7.96 (1H, dd, J=1.6, 8.4 Hz), 8.30 (1H, d, J=8.4 Hz), 8.64 (3H, bs).

Example 262

3-(Aminomethyl)-4-butoxy-6-(2-furyl)-2-isobutyl-1(2H)-isoquinolinone hydrochloride

(1) A solution of tert-butyl [6-bromo-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.48 g, 1 mmol), tri-n-butyl(2-furyl)tin (0.31 ml, 1 mmol) and tetrakis(triphenylphosphine)palladium (58 mg, 0.05 mmol) in tetrahydrofuran (20 ml) was refluxed at 80°C for 12 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [4-butoxy-6-(2-furyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.35 g, 76.1%) as crystals.

Melting point 157-158°C.

Elemental analysis for C₂₇H₃₆N₂O₅

Calculated: C, 69.21; H, 7.74; N, 5.98.

Found: C, 68.88; H, 7.98; N, 5.75.

¹H-NMR(CDCl₃) δ: 0.97 (6H, d, J=6.6 Hz), 1.06 (3H, t, J=7.3 Hz), 1.47 (9H, s), 1.57-1.70 (2H, m), 1.86-1.95 (2H, m), 2.14-2.23 (1H, m), 3.91 (2H, t, J=6.6 Hz), 3.99

(2H, d, J=7.2 Hz), 4.53 (2H, d, J=5.7 Hz), 4.78 (1H, bs), 6.54 (1H, dd, J=1.5, 3.3 Hz), 6.85 (1H, dd, J=0.6, 3.3 Hz), 7.56 (1H, dd, J=0.6, 1.5 Hz), 7.76 (1H, dd, J=1.5, 8.4 Hz), 7.97 (1H, d, J=1.5 Hz), 8.40 (1H, d, J=8.4 Hz).

5 (2) Tert-butyl [4-butoxy-6-(2-furyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.28 g, 0.6 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The solution was stirred at room temperature for 2 h. The reaction was 10 concentrated under reduced pressure, and the residue was crystallized from ethyl acetate - diisopropyl ether to give 3-(aminomethyl)-4-butoxy-6-(2-furyl)-2-isobutyl-1(2H)-isoquinolinone hydrochloride (0.22 g, 91.7%) as crystals.

15 Melting point 189-191°C.

Elemental analysis for C₂₂H₂₉N₂O₃Cl 1.75H₂O

Calculated: C, 60.54; H, 7.51; N, 6.42.

Found: C, 60.46; H, 7.07; N, 6.33.

1^H-NMR(DMSO-d₆) δ: 0.88 (6H, d, J=6.6 Hz), 1.02 (3H, t, 20 J=7.3 Hz), 1.51-1.69 (2H, m), 1.81-2.08 (3H, m), 3.93-3.99 (4H, m), 4.18 (2H, d, J=4.8 Hz), 6.99 (1H, dd, J=1.8, 3.3 Hz), 7.23 (1H, d, J=3.3 Hz), 7.90-7.97 (3H, m), 8.28 (1H, d, J=8.8 Hz), 8.75 (3H, bs).

Example 263

25 3-(Aminomethyl)-4-butoxy-2-isobutyl-6-phenyl-1(2H)-isoquinolinone hydrochloride

(1) A mixture of tert-butyl (6-bromo-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-

isoquinolinyl)methylcarbamate (0.48 g, 1 mmol),

30 phenylboric acid (0.15g, 1.2 mmol), sodium carbonate (0.26 g, 2.5 mmol), toluene (10 ml), ethanol (2 ml) and water (2 ml) was stirred at room temperature under an argon atmosphere for 30 min. To the resulting mixture was added tetrakis(triphenylphosphine)palladium (58 mg,

35 0.05 mmol), and then the mixture was refluxed under an argon atmosphere for 10 h. The reaction mixture was

5 poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl (4-butoxy-2-isobutyl-1-oxo-6-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.42 g, 89.4%) as crystals.

Melting point 155-159°C.

10 Elemental analysis for $C_{29}H_{38}N_2O_4$

Calculated: C, 72.77; H, 8.00; N, 5.85.

Found: C, 72.52; H, 7.81; N, 5.73.

1H -NMR(CDCl₃) δ: 0.98 (6H, d, J=6.6 Hz), 1.03 (3H, t, J=7.3 Hz), 1.47 (9H, s), 1.48-1.69 (2H, m), 1.81-1.95

15 (2H, m), 2.13-2.26 (1H, m), 3.92 (2H, t, J=6.6 Hz), 4.02 (2H, d, J=7.4 Hz), 4.55 (2H, d, J=5.4 Hz), 4.78 (1H, bs), 7.39-7.56 (3H, m), 7.66-7.75 (3H, m), 7.89 (1H, d, J=1.4 Hz), 8.49 (1H, d, J=8.6 Hz).

(2) Tert-butyl (4-butoxy-2-isobutyl-1-oxo-6-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.34 g, 0.7 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The solution was stirred at room temperature for 1 h. The reaction was concentrated under reduced pressure, and the residue was 25 crystallized from methanol - diisopropyl ether to give 3-(aminomethyl)-4-butoxy-2-isobutyl-6-phenyl-1(2H)-isoquinolinone hydrochloride (0.28 g, 96.6%) as crystals.

Melting point 180-181°C.

Elemental analysis for $C_{24}H_{31}N_2O_2Cl$

30 Calculated: C, 69.46; H, 7.53; N, 6.75.

Found: C, 69.15; H, 7.70; N, 6.81.

1H -NMR(DMSO-d₆) δ: 0.90 (6H, d, J=6.6 Hz), 1.00 (3H, t, J=7.4 Hz), 1.51-1.69 (2H, m), 1.80-2.12 (3H, m), 3.90-

35 4.05 (4H, m), 4.22 (2H, s), 7.45-7.62 (3H, m), 7.77-7.82 (2H, m), 7.91-7.95 (2H, m), 8.37 (1H, d, J=8.8 Hz), 8.71 (3H, bs).

Example 264

3-(Aminomethyl)-4-butoxy-2-isobutyl-6-[(E)-2-(1,3-

thiazol-4-yl)ethenyl]-1(2H)-isoquinolinone hydrochloride

(1) A mixture of triphenyl(1,3-thiazol-4-

5 ylmethyl)phosphonium chloride (0.44 g, 1.1 mmol), potassium carbonate (0.15 g, 1.1 mmol) and tert-butyl (4-butoxy-6-formyl-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.47 g, 1.1 mmol) in N,N-dimethylformamide (10 ml) was stirred at room
10 temperature for 10 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting crystals were recrystallized from ethyl acetate - diisopropyl ether to give tert-butyl {4-
15 butoxy-2-isobutyl-1-oxo-6-[(E)-2-(1,3-thiazol-4-yl)ethenyl]-1,2-dihydro-3-isoquinolinyl}methylcarbamate (0.46 g, 80.7%) as crystals.

Melting point 141-142°C.

20 Elemental analysis for C₂₉H₃₇N₃O₄S 0.5H₂O

Calculated: C, 65.39; H, 7.19; N, 7.89.

Found: C, 65.58; H, 7.33; N, 8.11.

¹H-NMR(CDCl₃) δ: 0.97 (6H, d, J=7.0 Hz), 1.06 (3H, t, J=7.3 Hz), 1.47 (9H, s), 1.48-1.69 (2H, m), 1.83-1.97 (2H, m), 2.11-2.25 (1H, m), 3.89 (2H, t, J=6.6 Hz), 3.99 (2H, d, J=7.4 Hz), 4.52 (2H, d, J=5.4 Hz), 4.77 (1H, bs), 7.31 (1H, d, J=16.0 Hz), 7.32 (1H, d, J=16.0 Hz), 7.32 (1H, d, J=1.8 Hz), 7.62-7.74 (3H, m), 8.39 (1H, d, J=8.8 Hz), 8.87 (1H, d, J=1.4 Hz).

30 (2) Tert-butyl {4-butoxy-2-isobutyl-1-oxo-6-[(E)-2-(1,3-thiazol-4-yl)ethenyl]-1,2-dihydro-3-isoquinolinyl}methylcarbamate (0.16 g, 0.3 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate solution (5 ml). The solution was stirred at
35 room temperature for 1 h. The reaction was concentrated under reduced pressure, and the residue was

recrystallized from methanol - diisopropyl ether to give 3-(aminomethyl)-4-butoxy-2-isobutyl-6-[(E)-2-(1,3-thiazol-4-yl)ethenyl]-1(2H)-isoquinolinone hydrochloride (0.11 g, 84.6%) as crystals.

5 Melting point 164-166°C.

Elemental analysis for $C_{24}H_{30}N_3O_2ClS$ 0.75H₂O

Calculated: C, 56.52; H, 6.42; N, 8.24.

Found: C, 56.44; H, 6.41; N, 8.21.

¹H-NMR(DMSO-d₆) δ: 0.89 (6H, d, J=6.6 Hz), 1.06 (3H, t,

10 J=7.1 Hz), 1.50-1.68 (2H, m), 1.83-2.10 (3H, m), 3.91-4.00 (4H, m), 4.18 (2H, d, J=4.4 Hz), 7.56 (1H, d, J=16.2 Hz), 7.67 (1H, d, J=16.2 Hz), 7.84 (1H, s), 7.87 (1H, d, J=1.8 Hz), 7.94 (1H, dd, J=1.8, 8.6 Hz), 8.26 (1H, d, J=8.6 Hz), 8.69 (3H, bs), 9.22 (1H, s).

15 Example 265

3-(Aminomethyl)-4-butoxy-2-isobutyl-6-[2-(1,3-thiazol-4-yl)ethyl]-1(2H)-isoquinolinone hydrochloride

(1) A suspension of tert-butyl {4-butoxy-2-isobutyl-1-oxo-6-[(E)-2-(1,3-thiazol-4-yl)ethenyl]-1,2-dihydro-3-

20 isoquinolinyl)methylcarbamate (0.21 g, 0.4 mmol) and 5% palladium carbon (0.2 g) in tetrahydrofuran (10 ml) was stirred under a hydrogen atmosphere at room temperature for 2 h. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The

25 residue was purified by silica gel column chromatography to give tert-butyl {4-butoxy-2-isobutyl-1-oxo-6-[2-(1,3-thiazol-4-yl)ethyl]-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.20 g, 95.2%) as crystals.

30 Melting point 103-104°C.

Elemental analysis for $C_{29}H_{35}N_2C_4S$ 0.5H₂O

Calculated: C, 65.14; H, 7.54; N, 7.86.

Found: C, 65.34; H, 7.53; N, 8.12.

¹H-NMR(CDCl₃) δ: 0.95 (6H, d, J=7.0 Hz), 1.04 (3H, t,

35 J=7.3 Hz), 1.46 (9H, s), 1.46-1.65 (2H, m), 1.77-1.91 (2H, m), 2.09-2.24 (1H, m), 3.22 (4H, s), 3.79 (2H, t,

J=6.6 Hz), 3.89 (2H, d, J=7.2 Hz), 4.50 (2H, d, J=5.6 Hz), 4.70 (1H, bs), 6.86 (1H, d, J=2.0 Hz), 7.33 (1H, dd, J=1.6, 8.2 Hz), 7.44 (1H, d, J=1.6 Hz), 8.33 (1H, d, J=8.2 Hz), 8.78 (1H, d, J=2.0 Hz).

5 (2) Tert-butyl {4-butoxy-2-isobutyl-1-oxo-6-[2-(1,3-thiazol-4-yl)ethyl]-1,2-dihydro-3-isoquinolinyl}methylcarbamate (0.16 g, 0.3 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The solution was stirred at room 10 temperature for 1 h. The reaction was concentrated under reduced pressure to give 3-(aminomethyl)-4-butoxy-2-isobutyl-6-[2-(1,3-thiazol-4-yl)ethyl]-1(2H)-isoquinolinone hydrochloride (0.13 g, 92.9%) as an amorphous solid.

15 Elemental analysis for C₂₄H₃₂N₃O₂ClS 2.5H₂O

Calculated: C, 56.85; H, 7.35; N, 8.29.

Found: C, 56.80; H, 7.20; N, 8.13.

¹H-NMR(DMSO-d₆) δ: 0.87 (6H, d, J=6.6 Hz), 1.00 (3H, t, J=7.3 Hz), 1.48-1.67 (2H, m), 1.77-1.87 (2H, m), 1.96-2.05 (1H, m), 3.16-3.21 (4H, m), 3.84 (2H, t, J=6.3 Hz), 3.94 (2H, d, J=6.0 Hz), 4.15 (2H, d, J=5.1 Hz), 7.35-7.38 (1H, m), 7.49-7.51 (2H, m), 8.18 (1H, d, J=8.7 Hz), 8.56 (3H, bs), 9.11-9.18 (1H, m).

Example 266

25 6-Amino-3-(aminomethyl)-4-butoxy-2-neopentyl-1(2H)-isoquinolinone dihydrochloride

(1) 9H-Fluoren-9-ylmethyl 4-butoxy-3-{{(tert-butoxycarbonyl)amino)methyl}-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinylcarbamate (1.14 g, 87.7%) as an 30 amorphous solid.

[synthesized according to the method similar to that in Example 82(1) from 4-butoxy-3-{{(tert-butoxycarbonyl)amino)methyl}-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid (0.92 g, 2 mmol)]

35 ¹H-NMR(CDCl₃) δ: 0.99 (9H, s), 1.01 (3H, t, J=7.4 Hz), 1.44 (9H, s), 1.45-1.62 (2H, m), 1.79-1.90 (2H, m), 3.86

(2H, t, J=6.4 Hz), 4.10 (2H, bs), 4.29 (1H, t, J=6.4 Hz), 4.54-4.62 (4H, m), 4.72 (1H, bs), 7.10 (1H, bs), 7.26-7.46 (5H, m), 7.63 (2H, d, J=7.3 Hz), 7.79 (2H, d, J=7.3 Hz), 8.78 (1H, s), 8.32 (1H, d, J=8.8 Hz).

- 5 (2) Tert-butyl (6-amino-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.66 g, 90.4%) as an amorphous solid.[synthesized according to the method similar to that in Example 82(2) from 9H-fluoren-9-ylmethyl 4-butoxy-3-{{(tert-
10 butoxycarbonyl)amino}methyl}-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinylcarbamate (1.11 g, 1.7 mmol)]
¹H-NMR(CDCl₃) δ: 0.98 (9H, s), 1.02 (3H, t, J=7.4 Hz), 1.44 (9H, s), 1.50-1.60 (2H, m), 1.70-1.88 (2H, m), 3.83 (2H, t, J=6.5 Hz), 4.19 (2H, bs), 4.53 (2H, d, J=5.4 Hz),
15 4.67 (1H, bs), 6.78-6.81 (2H, m), 8.20 (1H, d, J=9.0 Hz).
(3) 6-amino-3-(aminomethyl)-4-butoxy-2-neopentyl-1(2H)-isoquinolinone dihydrochloride (0.19 g, 95.0%) as an amorphous solid.[synthesized according to the method similar to that in Example 82(3) from tert-butyl (6-
20 amino-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.21 g, 0.5 mmol)].
Elemental analysis for C₁₉H₃₁N₃O₂Cl₂:
Calculated: C, 56.43; H, 7.73; N, 10.39.
Found: C, 56.71; H, 8.05; N, 10.00.
25 ¹H-NMR(DMSO-d₆) δ: 0.88 (9H, s), 1.02 (3H, t, J=6.2 Hz), 1.48-1.59 (2H, m), 1.77-1.91 (2H, m), 3.88 (2H, t, J=5.9 Hz), 4.00 (2H, bs), 4.19 (2H, bs), 6.53 (3H, bs), 6.98-7.04 (2H, m), 8.03 (1H, d, J=8.4 Hz), 8.54 (3H, bs).

Example 267

- 30 N-[3-(Aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinyl]acetamide hydrochloride
(1) Tert-butyl [6-(acetylamino)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.30 g, 63.8%) as crystals.[synthesized according to the method
35 similar to that in Example 88(1) from tert-butyl (6-amino-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-

isoquinolinyl)methylcarbamate (0.43 g, 1 mmol)]

Melting point 120-121°C.

¹H-NMR(CDCl₃) δ: 0.99 (9H, s), 1.01 (3H, t, J=7.0 Hz), 1.45 (9H, s), 1.47-1.66 (2H, m), 1.79-1.93 (2H, m), 2.26 5 (3H, s), 3.88 (2H, t, J=6.6 Hz), 4.14 (2H, bs), 4.56 (2H, d, J=5.6 Hz), 4.86 (1H, bs), 7.34 (1H, d, J=8.6 Hz), 7.88 (1H, bs), 8.15 (1H, s), 8.28 (1H, d, J=8.6 Hz). (2) N-[3-(Aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinyl]acetamide (0.19 g, 95.0%) as 10 crystals.

[synthesized according to the method similar to that in Example 88(2) from tert-butyl [6-(acetylamino)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.24 g, 0.5 mmol)]

15 Melting point 191-193°C.

Elemental analysis for C₂₁H₃₂N₃O₃Cl 0.5H₂O

Calculated: C, 60.20; H, 7.94; N, 10.03.

Found: C, 60.43; H, 8.07; N, 9.90.

¹H-NMR(DMSO-d₆) δ: 0.90 (9H, s), 0.99 (3H, t, J=6.2 Hz), 1.43-1.67 (2H, m), 1.72-1.93 (2H, m), 2.13 (3H, s), 3.92 20 (2H, s), 4.05 (2H, bs), 4.22 (2H, s), 7.70 (1H, d, J=8.6 Hz), 8.08 (1H, d, J=8.6 Hz), 8.27 (1H, s), 8.52 (3H, bs), 10.63 (1H, s).

Example 268

25 3-(Aminomethyl)-7-(benzyloxy)-2-isobutyl-4-phenyl-1(2H)-isoquinolinone hydrochloride

(1) Ethyl 7-(benzyloxy)-2-isobutyl-1-oxo-4-trifluoromethanesulfonyloxy-1,2-dihydro-3-isoquinolinecarboxylate (24.01 g, 91.0%) as crystals.

30 [synthesized according to the method similar to that in Example 154(2) from ethyl 7-(benzyloxy)-4-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (19.77 g, 50 mmol)]

¹H-NMR(CDCl₃) δ: 0.90 (6H, d, J=6.6 Hz), 1.44 (3H, t, J=7.1 Hz), 1.96-2.07 (1H, m), 4.12 (2H, d, J=7.2 Hz), 35 4.45 (2H, q, J=7.1 Hz), 5.21 (2H, s), 7.30-7.48 (6H, m),

- 7.74 (1H, d, J=9.0 Hz), 7.96 (1H, d, J=9.0 Hz).
(2) Ethyl 7-(benzyloxy)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinecarboxylate (16.21 g, 79.1%) as crystals.
- 5 [synthesized according to the method similar to that in Example 154(3) from ethyl 7-(benzyloxy)-2-isobutyl-1-oxo-4-trifluoromethanesulfonyloxy-1,2-dihydro-3-isoquinolinecarboxylate (23.74 g, 45 mmol) and phenylboronic acid (6.58 g, 54 mmol)]
- 10 Melting point 107-108°C.
Elemental analysis for $C_{29}H_{29}NO_4$
Calculated: C, 76.46; H, 6.42; N, 3.07.
Found: C, 76.45; H, 6.54; N, 3.06.
 1H -NMR(CDCl₃) δ: 0.87 (3H, d, J=7.2 Hz), 0.94 (6H, d, J=6.6 Hz), 2.05-2.23 (1H, m), 3.93 (2H, q, J=7.2 Hz), 4.05 (2H, d, J=7.4 Hz), 5.21 (2H, s), 7.13-7.50 (12H, m), 8.03 (1H, d, J=2.2 Hz).
- 15 (3) 7-(Benzylloxy)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinecarboxylic acid (11.21 g, 74.9%) as an amorphous solid.
- 20 [synthesized according to the method similar to that in Example 154(4) from ethyl 7-(benzyloxy)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinecarboxylate (15.94 g, 35 mmol)]
- 25 1H -NMR(CDCl₃) δ: 0.90 (6H, d, J=6.8 Hz), 2.14-2.28 (1H, m), 4.01 (2H, d, J=7.8 Hz), 5.15 (2H, s), 7.11-7.48 (12H, m), 7.66 (1H, d, J=1.8 Hz).
- 30 (4) 7-(Benzylloxy)-3-(hydroxymethyl)-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (9.31 g, 90.1%) as crystals.
- 35 [synthesized according to the method similar to that in Example 154(5) from 7-(benzyloxy)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinecarboxylic acid (10.69 g, 25 mmol)]
- Melting point 125-126°C.
Elemental analysis for $C_{27}H_{27}NO_3 \cdot 0.5H_2O$
Calculated: C, 76.75; H, 6.68; N, 3.32.

Found: C, 76.36; H, 6.46; N, 3.24.

¹H-NMR(CDCl₃) δ: 0.99 (6H, d, J=7.0 Hz), 2.05 (1H, bs), 2.20-2.34 (1H, m), 4.25 (2H, d, J=7.2 Hz), 4.46 (2H, d, J=3.6 Hz), 5.11 (2H, s), 6.92 (1H, d, J=8.8 Hz), 7.11 (1H, dd, J=2.6, 8.8 Hz), 7.29-7.56 (10H, m), 7.91 (1H, d, J=2.6 Hz).

(5) 7-(Benzylxy)-3-(chloromethyl)-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (7.44 g, 86.2%) as an oil.

[synthesized according to the method similar to that in Example 154(6) from 7-(benzylxy)-3-(hydroxymethyl)-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (8.27 g, 20 mmol)]

¹H-NMR(CDCl₃) δ: 1.02 (6H, d, J=7.0 Hz), 2.16-2.31 (1H, m), 4.20. (2H, d, J=7.4 Hz), 4.42 (2H, s), 5.20 (2H, s), 6.96 (1H, d, J=8.8 Hz), 7.13-7.54 (11H, m), 8.01 (1H, d, J=2.8 Hz).

(6) 2-{[7-(Benzylxy)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methyl}-1H-isoindole-1,3(2H)-dione (8.74 g, 94.8%) as an amorphous solid.

[synthesized according to the method similar to that in Example 154(7) from 7-(benzylxy)-3-(chloromethyl)-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (7.34 g, 17 mmol)]

¹H-NMR(CDCl₃) δ: 1.01 (6H, d, J=6.6 Hz), 2.17-2.31 (1H, m), 4.08 (2H, d, J=7.0 Hz), 4.78 (2H, s), 5.19 (2H, s), 6.92 (1H, d, J=9.0 Hz), 7.17 (1H, dd, J=2.8; 9.0 Hz), 7.21-7.49 (10H, m), 7.66-7.78 (4H, m), 7.98 (1H, d, J=2.8 Hz).

(7) Tert-butyl [7-(benzylxy)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (7.56 g, 92.2%) as crystals.

[synthesized according to the method similar to that in Example 154(8) from 2-{[7-(benzylxy)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methyl}-1H-isoindole-1,3(2H)-dione (8.68 g, 16 mmol)]

Melting point 181-182°C.

Elemental analysis for $C_{32}H_{36}N_2O_4$

Calculated: C, 74.97; H, 7.08; N, 5.46.

Found: C, 74.94; H, 7.14; N, 5.31.

- ¹H-NMR(CDCl₃) δ: 1.01 (6H, d, J=6.8 Hz), 1.43 (9H, s),
 5 2.20-2.31 (1H, m), 4.08 (2H, d, J=7.4 Hz), 4.19 ((2H, d,
 J=5.2 Hz), 4.55 (1H, bs), 5.16 (2H, s), 6.89 (1H, d,
 J=8.8 Hz), 7.15 (1H, dd, J=2.8, 8.8 Hz), 7.24-7.55 (10H,
 m), 7.96 (1H, d, J=2.8 Hz).
- (8) 3-(Aminomethyl)-7-(benzyloxy)-2-isobutyl-4-phenyl-
 10 1(2H)-isoquinolinone hydrochloride (0.21 g, 95.5%) as
 crystals.

[synthesized according to the method similar to that in
 Example 214(3) from tert-butyl [7-(benzyloxy)-2-
 isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-

- 15 isoquinolinyl]methylcarbamate (0.26 g, 0.5 mmol)]

Melting point 242-243°C.

Elemental analysis for $C_{27}H_{29}N_2O_2Cl$

Calculated: C, 72.23; H, 6.51; N, 6.24.

Found: C, 71.99; H, 6.54; N, 6.05.

- 20 ¹H-NMR(DMSO-d₆) δ: 0.92 (6H, d, J=6.6 Hz), 1.99-2.19 (1H,
 m), 3.85 (2H, d, J=4.8 Hz), 4.09 (2H, s), 5.26 (2H, s),
 6.85 (1H, d, J=8.8 Hz), 7.33-7.57 (11H, m), 7.85 (1H, d,
 J=2.6 Hz), 8.58 (3H, bs).

Example 269

- 25 3-(Aminomethyl)-7-hydroxy-2-isobutyl-4-phenyl-1(2H)-
 isoquinolinone hydrochloride

(1) Tert-butyl (7-hydroxy-2-isobutyl-1-oxo-4-phenyl-1,2-
 dihydro-3-isoquinolinyl)methylcarbamate (5.75 g, 97.3%)
 as crystals.

- 30 [synthesized according to the method similar to that in
 Example 154(9) from tert-butyl [7-(benzyloxy)-2-
 isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-
 isoquinolinyl]methylcarbamate (7.14 g, 14 mmol)]

Melting point 232-233°C.

- 35 Elemental analysis for $C_{25}H_{30}N_2O_4$

Calculated: C, 71.07; H, 7.16; N, 6.63.

Found: C, 70.81; H, 7.22; N, 6.35.

¹H-NMR(CDCl₃) δ: 1.02 (6H, d, J=7.0 Hz), 1.42 (9H, s), 2.21-2.35 (1H, m), 4.11 (2H, d, J=7.2 Hz), 4.22 (2H, d, J=5.2 Hz), 4.52 (1H, bs), 6.91 (1H, d, J=8.8 Hz), 7.16 (1H, dd, J=2.6, 8.8 Hz), 7.23-7.28 (2H, m), 7.44-7.55 (3H, m), 8.52 (1H, d, J=2.8 Hz), 8.90 (1H, s).

(2) 3-(Aminomethyl)-7-hydroxy-2-isobutyl-4-phenyl-1(2H)-isoquinolinone hydrochloride (0.17 g, 94.4%) as crystals.

[synthesized according to the method similar to that in Example 214(3) from tert-butyl (7-hydroxy-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.21 g, 0.5 mmol)]

Melting point 259-261°C.

Elemental analysis for C₂₀H₂₃N₂O₂Cl 0.25H₂O

Calculated: C, 66.11; H, 6.52; N, 7.71.

Found: C, 66.00; H, 6.51; N, 7.53.

¹H-NMR(DMSO-d₆) δ: 0.91 (6H, d, J=6.6 Hz), 2.00-2.16 (1H, m), 3.85 (2H, s), 4.05 (2H, d, J=7.0 Hz), 6.76 (1H, d, J=8.8 Hz), 7.13 (1H, dd, J=2.8, 8.8 Hz), 7.35-7.39 (2H, m), 7.47-7.60 (2H, m), 7.68 (1H, d, J=2.8 Hz), 8.48 (3H, bs), 10.27 (1H, bs).

Example 270

3-(Aminomethyl)-7-ethoxy-2-isobutyl-4-phenyl-1(2H)-isoquinolinone hydrochloride

(1) Tert-butyl (7-ethoxy-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.39 g, 86.7%) as crystals.

[synthesized according to the method similar to that in Example 154(10) from tert-butyl (7-hydroxy-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.42 g, 1 mmol) and 2-iodoethane (0.12 ml, 1.5 mmol)]

Melting point 163-164°C.

Elemental analysis for C₂₇H₃₄N₂O₄

Calculated: C, 71.97; H, 7.61; N, 6.22.

Found: C, 71.67; H, 7.41; N, 6.28.

¹H-NMR(CDCl₃) δ: 1.01 (6H, d, J=6.6 Hz), 1.42 (9H, s),

1.44 (3H, t, J=7.4 Hz), 2.19-2.35 (1H, m), 4.06-4.21 (6H, m), 4.48 (1H, bs), 6.88 (1H, d, J=9.0 Hz), 7.09 (1H, dd, J=2.7, 9.0 Hz), 7.23-7.27 (2H, m), 7.46-7.53 (3H, m), 7.86 (1H, d, J=2.6 Hz).

- 5 (2) 3-(Aminomethyl)-7-ethoxy-2-isobutyl-4-phenyl-1(2H)-isoquinolinone hydrochloride (0.18 g, 66.7%) as crystals.
 [synthesized according to the method similar to that in Example 214(3) from tert-butyl (7-ethoxy-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate

10 (0.32 g, 0.7 mmol)]

Melting point 154-155°C.

Elemental analysis for $C_{22}H_{27}N_2O_2Cl$ 0.25H₂O

Calculated: C, 67.51; H, 7.08; N, 7.16.

Found: C, 67.30; H, 7.04; N, 7.10.

15 ¹H-NMR(DMSO-d₆) δ: 0.92 (6H, d, J=6.6 Hz), 1.37 (3H, t, J=6.8 Hz), 2.01-2.19 (1H, m), 3.86 (2H, s), 4.07-4.20 (4H, m), 6.83 (1H, d, J=9.0 Hz), 7.27 (1H, dd, J=2.8, 9.0 Hz), 7.37-7.41 (2H, m), 7.54-7.57 (3H, m), 7.73 (1H, d, J=2.8 Hz), 8.53 (3H, s).

20 Example 271

3-(Aminomethyl)-2-isobutyl-7-(2-methoxyethoxy)-4-phenyl-1(2H)-isoquinolinone hydrochloride

(1) Tert-butyl [2-isobutyl-7-(2-methoxyethoxy)-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.34

25 g, 70.8%) as crystals.

[synthesized according to the method similar to that in Example 154(10) from tert-butyl (7-hydroxy-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.42 g, 1 mmol) and bromoethyl methyl ether (0.14 ml,

30 1.5 mmol)]

Melting point 124-125°C.

Elemental analysis for $C_{28}H_{36}N_2O_5$

Calculated: C, 69.98; H, 7.55; N, 5.83.

Found: C, 69.81; H, 7.37; N, 5.96.

35 ¹H-NMR(CDCl₃) δ: 1.00 (6H, d, J=6.6 Hz), 1.42 (9H, s), 2.19-2.35 (1H, m), 3.45 (3H, s), 3.74-3.80 (2H, m), 4.08

(2H, d, J=7.0 Hz), 4.19-4.27 (4H, m), 4.51 (1H, bs),
6.89 (1H, d, J=8.6 Hz), 7.16 (1H, dd, J=2.8, 8.6 Hz),
7.19-7.27 (2H, m), 7.47-7.52 (3H, m), 7.86 (1H, d, J=2.8
Hz).

- 5 (2) 3-(Aminomethyl)-2-isobutyl-7-(2-methoxyethoxy)-4-phenyl-1(2H)-isoquinolinone hydrochloride (0.21 g, 84.0%) as crystals.

[synthesized according to the method similar to that in Example 214(3) from tert-butyl [2-isobutyl-7-(2-methoxyethoxy)-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.28 g, 0.6 mmol)]

Melting point 148-149°C.

Elemental analysis for C₂₃H₂₉N₂O₃Cl 0.5H₂O

Calculated: C, 64.85; H, 7.10; N, 6.58.

15 Found: C, 65.25; H, 7.21; N, 6.73.

¹H-NMR(DMSO-d₆) δ: 0.92 (6H, d, J=6.2 Hz), 1.99-2.21 (1H, m), 3.31 (3H, s), 3.63-3.69 (2H, m), 3.86 (2H, s), 4.07-4.10 (2H, m), 4.22 (2H, s), 6.84 (1H, d, J=9.2 Hz), 7.28-7.40 (3H, m), 7.54-7.62 (3H, m), 7.74 (1H, s), 8.56
20 (3H, s).

Example 272

2-{{[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-7-isoquinolinyl]oxy}acetamide hydrochloride

(1) Tert-butyl [7-(2-amino-2-oxoethoxy)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.19 g, 40.4%) as crystals.

[synthesized according to the method similar to that in Example 154(10) from tert-butyl (7-hydroxy-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.42 g, 1 mmol) and 2-iodoacetamide (0.27 g, 1.5 mmol)]

Melting point 211-212°C.

Elemental analysis for C₂₇H₃₃N₃O₅

Calculated: C, 67.62; H, 6.94; N, 8.76.

Found: C, 67.38; H, 6.69; N, 8.87.

35 ¹H-NMR(CDCl₃) δ: 1.00 (6H, d, J=6.6 Hz), 1.43 (9H, s), 2.18-2.34 (1H, m), 4.08 (2H, d, J=7.4 Hz), 4.20 (2H, d,

$J=5.4$ Hz), 4.51 (1H, bs), 4.58 (2H, s), 5.86 (1H, bs), 6.57 (1H, bs), 6.94 (1H, d, $J=8.8$ Hz), 7.13 (1H, d, $J=8.8$ Hz), 7.23-7.27 (2H, m), 7.49-7.52 (3H, m), 7.90 (1H, s).

- 5 (2) 2-{[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-7-isoquinolinyl]oxy}acetamide hydrochloride (0.11 g, 91.2%) as crystals. [synthesized according to the method similar to that in Example 214(3) from tert-butyl [7-(2-amino-2-oxoethoxy)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.14 g, 0.3 mmol)] Melting point 244-245°C.
Elemental analysis for $C_{22}H_{26}N_3O_3Cl$ 1.75H₂O
Calculated: C, 59.06; H, 6.65; N, 9.39.
Found: C, 59.21; H, 6.52; N, 9.33.
- 10 15 ¹H-NMR(DMSO-d₆) δ: 0.92 (6H, d, $J=6.6$ Hz), 1.99-2.19 (1H, m), 3.85 (2H, d, $J=4.2$ Hz), 4.09 (2H, d, $J=7.0$ Hz), 4.58 (2H, s), 6.85 (1H, d, $J=8.8$ Hz), 7.33 (1H, dd, $J=2.6$, 8.8 Hz), 7.36-7.41 (2H, m), 7.56-7.60 (3H, m), 7.69 (1H, bs), 7.72 (1H, d, $J=2.6$ Hz), 8.64 (3H, s).

20 Example 273

3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-7-isoquinolinecarboxamide hydrochloride

(1) Tert-butyl (2-isobutyl-1-oxo-4-phenyl-7-trifluoromethanesulfonyloxy-1,2-dihydro-3-

25 isoquinolinyl)methylcarbamate (5.01 g, 90.4%) as an amorphous solid. [synthesized according to the method similar to that in Example 155(1) from tert-butyl (7-hydroxy-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (4.22 g, 10 mmol)]

30 ¹H-NMR(CDCl₃) δ: 1.01 (6H, d, $J=6.6$ Hz), 1.43 (9H, s), 2.20-2.29 (1H, m), 4.09 (2H, d, $J=7.5$ Hz), 4.23 (2H, d, $J=5.4$ Hz), 4.46 (1H, bs), 7.06 (1H, d, $J=9.0$ Hz), 7.22-7.27 (2H, m), 7.36 (1H, dd, $J=2.7$, 9.0 Hz), 7.42-7.56 (3H, m), 8.34 (1H, d, $J=2.7$ Hz).

35 (2) Methyl 3-[(tert-butoxycarbonyl)amino]methyl-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-7-

- isoquinolinecarboxylate (3.11 g, 74.4%) as crystals.
[synthesized according to the method similar to that in Example 155(2) from tert-butyl (2-isobutyl-1-oxo-4-phenyl-7-trifluoromethanesulfonyloxy-1,2-dihydro-3-isoquinolinyl)methylcarbamate (4.99 g, 9 mmol)]
Melting point 134-135°C.
Elemental analysis for C₂₇H₃₂N₂O₅
Calculated: C, 69.81; H, 6.94; N, 6.03.
Found: C, 69.46; H, 7.04; N, 5.81.
- 10 ¹H-NMR(CDCl₃) δ: 1.01 (6H, d, J=6.6 Hz), 1.43 (9H, s), 2.05-2.28 (1H, m), 3.93 (3H, s), 4.10 (2H, d, J=7.5 Hz), 4.22 (2H, d, J=5.4 Hz), 4.61 (1H, bs), 6.98 (1H, d, J=8.7 Hz), 7.24-7.28 (2H, m), 7.46-7.57 (3H, m), 8.02 (1H, dd, J=1.8, 8.7 Hz), 9.10 (1H, d, J=1.8 Hz).
- 15 (3) 3-{[(Tert-butoxycarbonyl)amino]methyl}-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-7-isoquinolinecarboxylic acid (2.49 g, 92.2%) as crystals.
[synthesized according to the method similar to that in Example 155(3) from methyl 3-{[(tert-butoxycarbonyl)amino]methyl}-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-7-isoquinolinecarboxylate (2.79 g, 6 mmol)]
Melting point 246°C.
Elemental analysis for C₂₆H₃₀N₂O₅ 0.25H₂O
Calculated: C, 68.62; H, 6.76; N, 6.16.
25 Found: C, 68.88; H, 6.83; N, 5.87.
¹H-NMR(CDCl₃) δ: 0.91 (6H, d, J=6.6 Hz), 1.38 (9H, s), 2.12-2.26 (1H, m), 3.91 (2H, d, J=6.6 Hz), 3.99 (2H, d, J=4.2 Hz), 6.99 (1H, d, J=8.8 Hz), 7.34 (1H, bs), 7.39-7.42 (2H, m), 7.46-7.56 (3H, m), 8.09 (1H, dd, J=2.0, 8.8 Hz), 8.87 (1H, d, J=2.0 Hz).
(4) Tert-butyl [7-(aminocarbonyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.86 g, 95.6%) as crystals. [synthesized according to the method similar to that in Example 155(4) from 3-{[(tert-butoxycarbonyl)amino]methyl}-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-7-isoquinolinecarboxylic acid (0.90 g, 2

mmol)]

Melting point 232-233°C.

Elemental analysis for C₂₆H₃₁N₃O₄ 0.5H₂O

Calculated: C, 68.10; H, 7.03; N, 9.16.

5 Found: C, 68.31; H, 7.07; N, 8.75.

¹H-NMR(CDCl₃) δ: 0.99 (6H, d, J=6.6 Hz), 1.43 (9H, s), 2.10-2.24 (1H, m), 4.08 (2H, d, J=7.0 Hz), 4.22 (2H, d, J=5.2 Hz), 4.76 (1H, bs), 5.96 (1H, bs), 6.74 (1H, bs), 7.02 (1H, d, J=8.6 Hz), 7.25-7.30 (2H, m), 7.45-7.56 (3H,

10 m), 8.05 (1H, dd, J=1.4, 8.6 Hz), 8.78 (1H, d, J=1.4 Hz).

(5) 3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-7-isoquinolinecarboxamide hydrochloride (0.18 g, 94.7%) as crystals. [synthesized according to the method similar to that in Example 155(5) from tert-butyl [7-

15 (aminocarbonyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.23 g, 0.5 mmol)]

Melting point 254-256°C.

Elemental analysis for C₂₁H₂₄N₃O₂Cl H₂O

Calculated: C, 63.87; H, 6.38; N, 10.64.

20 Found: C, 63.76; H, 6.29; N, 10.30.

¹H-NMR(DMSO-d₆) δ: 0.94 (6H, d, J=6.6 Hz), 2.04-2.19 (1H, m), 3.89 (2H, d, J=4.4 Hz), 4.13 (2H, d, J=7.0 Hz), 6.94 (1H, d, J=8.6 Hz), 7.37-7.44 (2H, m), 7.54-7.64 (4H, m), 8.16 (1H, dd, J=1.8, 8.6 Hz), 8.30 (1H, bs), 8.67 (3H, bs), 8.85 (1H, d, J=1.8 Hz).

Example 274

3-[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]propanamide hydrochloride

(1) A suspension of ethyl (E)-3-(3-{[(tert-

30 butoxycarbonyl)amino]methyl}-2-isobutyl-1-oxo-4-phenyl-

1,2-dihydro-6-isoquinolinyl)-2-propenoate (0.90g, 1.8

mmol) and 5% palladium carbon (0.5 g) in ethanol (10 ml) and tetrahydrofuran (10 ml) was stirred under a hydrogen atmosphere at room temperature for 2 h. The catalyst was

35 filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel

column chromatography to give ethyl 3-(3-{[(tert-butoxycarbonyl)amino]methyl}-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl)propanoate (0.82 g, 90.1%) as an amorphous solid.

5 ¹H-NMR(CDCl₃) δ: 0.99 (6H, d, J=6.6 Hz), 1.19 (3H, t, J=7.1 Hz), 1.42 (9H, s), 2.18-2.29 (1H, m), 2.51 (2H, t, J=7.8 Hz), 2.90 (2H, t, J=7.8 Hz), 4.01-4.12 (4H, m), 4.19 (2H, d, J=5.6 Hz), 4.40 (1H, bs), 6.74 (1H, d, J=1.6 Hz), 7.21-7.26 (2H, m), 7.31 (1H, dd, J=1.6, 8.4

10 Hz), 7.46-7.53 (3H, m), 8.39 (1H, d, J=8.4 Hz).

(2) To a solution of ethyl 3-(3-{[(tert-butoxycarbonyl)amino]methyl}-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl)propanoate (0.61g, 1.2 mmol) in tetrahydrofuran (5 ml) and ethanol (5 ml) was added 15 1N sodium hydroxide solution (3 ml). The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous 20 magnesium sulfate and concentrated under reduced pressure. The resulting crystals were recrystallized from ethyl acetate - diisopropyl ether to give 3-(3-{[(tert-butoxycarbonyl)amino]methyl}-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl)propanoic acid (0.52 25 g, 91.2%) as crystals.

Melting point 182-183°C.

Elemental analysis for C₂₈H₃₄N₂O₅

Calculated: C, 70.12; H, 7.36; N, 5.84.

Found: C, 70.21; H, 7.55; N, 5.68.

30 ¹H-NMR(CDCl₃) δ: 0.98 (6H, d, J=6.9 Hz), 1.42 (9H, s), 2.15-2.27 (1H, m), 2.58 (2H, t, J=7.8 Hz), 2.91 (2H, t, J=7.8 Hz), 4.06 (2H, d, J=6.0 Hz), 4.19 (2H, d, J=5.2 Hz), 4.53 (1H, bs), 6.76 (1H, s), 7.22-7.25 (2H, m), 7.31 (1H, d, J=8.8 Hz), 7.46-7.52 (3H, m), 8.37 (1H, d, 35 J=8.8 Hz).

(3) A solution of 3-(3-{[(tert-

butoxycarbonyl)amino]methyl}-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]propanoic acid (0.33 g, 0.7 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.27 g, 1.4 mmol) and 1-hydroxybenzotriazole ammonium salt (0.21 g, 1.4 mmol) in N,N-dimethylformamide (10 ml) was stirred at room temperature for 2 h. The resulting reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [6-(3-amino-3-oxopropyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.31 g, 93.9%) as crystals.

Melting point 239-240°C.

Elemental analysis for C₂₈H₃₅N₃O₄ 0.25H₂O

Calculated: C, 69.76; H, 7.42; N, 8.72.

Found: C, 69.54; H, 7.41; N, 8.58.

¹H-NMR(CDCl₃) δ: 0.99 (6H, d, J=6.6 Hz), 1.42 (9H, s), 2.13-2.29 (1H, m), 2.43 (2H, t, J=8.0 Hz), 2.92 (2H, t, J=8.0 Hz), 4.05 (2H, d, J=7.4 Hz), 4.19 (2H, d, J=5.2 Hz), 4.54 (1H, bs), 5.42 (2H, bs), 6.75 (1H, d, J=1.4 Hz), 7.21-7.30 (3H, m), 7.21-7.30 (3H, m), 7.46-7.57 (3H, m), 8.33-8.37 (1H, m).

(4) 3-[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]propanamide hydrochloride (0.20 g, 95.3%), as crystals. [synthesized according to the method similar to that in Example 214(3) from tert-butyl [6-(3-amino-3-oxopropyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.24 g, 0.5 mmol)]

Melting point 186-187°C.

¹H-NMR(DMSO-d₆) δ: 0.91 (6H, d, J=6.6 Hz), 2.02-2.16 (1H, m), 2.26 (2H, t, J=7.2 Hz), 2.76 (2H, t, J=7.2 Hz), 3.86 (2H, s), 4.08 (2H, s), 6.72 (1H, s), 6.75 (1H, bs), 7.29

(1H, bs), 7.38-7.40 (2H, m), 7.45 (1H, d, J=8.4 Hz), 7.55-7.59 (3H, m), 8.25 (1H, d, J=8.4 Hz), 8.57 (3H, bs).

Example 275

5 2-(2-{[3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]oxy}ethyl)-1H-isoindole-1,3(2H)-dione hydrochloride

To a solution of tert-butyl (4-butoxy-6-hydroxy-2-isobutyl-1-oxo-4-1,2-dihydro-3-isoquinolinyl)methylcarbamate (2.09 g, 5 mmol), N-(2-hydroxyethyl)phthalimide (1.15 g, 6 mmol) and tri-n-butylphosphine (2.5 ml, 10 mmol) in tetrahydrofuran (30 ml) was added 1,1'-(azodicarbonyl)dipiperidine (2.52 g, 10 mmol), and the mixture was stirred at room temperature for 6 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography. The resulting crystals were dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The solution was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the residue was crystallized from methanol - diisopropyl ether to give 2-(2-{[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]oxy}ethyl)-1H-isoindole-1,3(2H)-dione hydrochloride (0.14 g, 93.3%) as crystals.

Melting point 176-177°C.

¹H-NMR(DMSO-d₆) δ: 0.86 (6H, d, J=6.6 Hz), 0.99 (3H, t, J=7.3 Hz), 1.46-1.64 (2H, m), 1.77-2.06 (3H, m), 3.88-3.94 (4H, m), 4.04 (2H, t, J=5.5 Hz), 4.15 (2H, s), 4.41 (2H, t, J=5.5 Hz), 7.05 (1H, d, J=2.4 Hz), 7.14 (1H, dd, J=2.4, 9.0 Hz), 7.82-7.92 (4H, m), 8.15 (1H, d, J=9.0 Hz), 8.53 (3H, bs).

Example 276

3-[3-(Aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinyl]propanamide hydrochloride

35 (1) Ethyl 3-(3-{{(tert-butoxycarbonyl)amino}methyl}-4-

- butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinyl)propanoate (0.68 g, 88.3%) as an oil.
[synthesized according to the method similar to that in Example 274(1) from ethyl (E)-3-{[(tert-
5 butoxycarbonyl)amino]methyl}-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinyl)-2-propenoate (0.77 g, 1.5 mmol)]
- ¹H-NMR(CDCl₃) δ: 0.99 (9H, s), 1.04 (3H, t, J=7.2 Hz), 1.24 (3H, t, J=7.0 Hz), 1.45 (9H, s), 1.49-1.68 (2H, m),
10 1.80-1.94 (2H, m), 2.70 (2H, t, J=7.8 Hz), 3.11 (2H, t, J=7.8 Hz), 3.86 (2H, t, J=6.6 Hz), 4.10 (2H, bs), 4.14 (2H, q, J=7.0 Hz), 4.58 (2H, s), 4.62 (1H, bs), 7.35 (1H, dd, J=1.6, 8.2 Hz), 7.51 (1H, d, J=1.6 Hz), 8.33 (1H, d, J=8.4 Hz).
- 15 (2) 3-(3-{[(Tert-butoxycarbonyl)amino]methyl}-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinyl)propanoic acid (0.40 g, 90.9%) as crystals.
[synthesized according to the method similar to that in Example 274(2) from ethyl 3-(3-{[(tert-
20 butoxycarbonyl)amino]methyl}-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinyl)propanoate (0.46g, 0.9 mmol)]
- ¹H-NMR(CDCl₃) δ: 0.98 (9H, s), 1.03 (3H, t, J=7.4 Hz), 1.45 (9H, s), 1.46-1.67 (2H, m), 1.79-1.92 (2H, m), 2.77
25 (2H, t, J=7.4 Hz), 3.11 (2H, t, J=7.4 Hz), 3.84 (2H, t, J=6.4 Hz), 4.14 (2H, bs), 4.57 (2H, d, J=5.8 Hz), 4.75 (1H, bs), 7.34 (1H, dd, J=1.6, 8.5 Hz), 7.52 (1H, d, J=1.6 Hz), 8.32 (1H, d, J=8.5 Hz).
- (3) Tert-butyl [6-(3-amino-3-oxopropyl)-4-butoxy-2-
30 neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.19 g, 86.4%) as crystals.
[synthesized according to the method similar to that in Example 274(3) from 3-(3-{[(tert-
35 butoxycarbonyl)amino]methyl}-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinyl)propanoic acid (0.22 g, 0.45

mmol)]

Melting point 87-88°C.

Elemental analysis for C₂₇H₄₁N₃O₅

Calculated: C, 66.50; H, 8.47; N, 8.62.

5 Found: C, 66.25; H, 8.35; N, 8.54.

¹H-NMR(CDCl₃) δ: 0.99 (9H, s), 1.04 (3H, t, J=7.4 Hz), 1.45 (9H, s), 1.52-1.72 (2H, m), 1.80-1.94 (2H, m), 2.60 (2H, t, J=7.7 Hz), 3.13 (2H, t, J=7.7 Hz), 3.86 (2H, t, J=6.6 Hz), 4.14 (2H, bs), 4.56 (2H, d, J=5.4 Hz); 4.73

10 (1H, bs), 5.50 (2H, bs), 7.32 (1H, d, J=8.2 Hz), 7.52 (1H, s), 8.29 (1H, d, J=8.2 Hz).

(4) 3-[3-(Aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isooquinolinyl]propanamide hydrochloride (0.11 g, 91.7%) as crystals. [synthesized according to the 15 method similar to that in Example 274(4) from tert-butyl [6-(3-amino-3-oxopropyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isooquinolinyl]methylcarbamate (0.14 g, 0.3 mmol)]

Melting point 151-153°C.

20 Elemental analysis for C₂₇H₄₁N₃O₅Cl

Calculated: C, 66.50; H, 8.47; N, 8.62.

Found: C, 66.25; H, 8.35; N, 8.54.

¹H-NMR(DMSO-d₆) δ: 0.90 (9H, s), 1.00 (3H, t, J=7.3 Hz), 1.51-1.62 (2H, m), 1.78-1.91 (2H, m), 2.46 (2H, t, J=7.4 Hz), 3.00 (2H, t, J=7.4 Hz), 3.93 (2H, t, J=6.1 Hz), 4.08 (2H, bs), 4.23 (2H, d, J=4.0 Hz), 6.82 (1H, bs), 7.44 (1H, bs), 7.47 (1H, d, J=8.2 Hz), 7.58 (1H, s), 8.17 (1H, d, J=8.2 Hz), 8.53 (3H, bs).

Example 277

30 [3-(Aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isooquinolinyl]acetonitrile hydrochloride

(1) To a solution of p-toluenesulfonylmethyl isocyanide (0.94 g, 4.8 mmol) in 1,2-dimethoxyethane (20 ml) were added potassium t-butoxide (0.90 g, 8 mmol) and tert-

35 butyl (4-butoxy-6-formyl-2-neopentyl-1-oxo-1,2-dihydro-3-isooquinolinyl)methylcarbamate (1.78 g, 4 mmol) at -

70°C, and the mixture was stirred at -70°C for 1 h. To the mixture was added methanol (30 ml), and the mixture was refluxed for 30 min. The reaction mixture was poured into water and extracted with ethyl acetate. The extract 5 was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [4-butoxy-6-(cyanomethyl)-2-neopentyl-1-oxo-1,2-dihydro-3-

10 isoquinolinyl]methylcarbamate (0.66 g, 36.3%) as an amorphous solid.

¹H-NMR(CDCl₃) δ: 1.00 (9H, s), 1.04 (3H, t, J=7.4 Hz), 1.45 (9H, s), 1.51-1.66 (2H, m), 1.82-1.92 (2H, m), 3.88 (2H, t, J=6.2 Hz), 3.92 (2H, s), 4.18 (2H, bs), 4.58 (2H, d, J=5.0 Hz), 4.72 (1H, bs), 7.40 (1H, dd, J=1.8, 8.4 Hz), 7.70 (1H, d, J=1.8 Hz), 8.40 (1H, d, J=8.4 Hz).

(2) [3-(Aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isooquinolinyl]acetonitrile hydrochloride (0.10 g, 90.9%) as crystals [synthesized according to the 15 method similar to that in Example 214(3) from tert-butyl [4-butoxy-6-(cyanomethyl)-2-neopentyl-1-oxo-1,2-dihydro-3-isooquinolinyl]methylcarbamate (0.14 g, 0.3 mmol)].

Melting point 169-171°C.

Elemental analysis for C₂₁H₃₀N₃O₂Cl 0.25H₂O

Calculated: C, 63.62; H, 7.73; N, 10.60.

Found: C, 63.70; H, 7.85; N, 10.59.

¹H-NMR(DMSO-d₆) δ: 0.90 (9H, s), 1.00 (3H, t, J=7.4 Hz), 1.52-1.63 (2H, m), 1.80-1.91 (2H, m), 3.94 (2H, t, J=6.6 Hz), 4.14 (2H, bs), 4.26 (2H, bs), 4.33 (2H, s), 7.57 (1H, dd, J=1.4, 8.0 Hz), 7.78 (1H, d, J=1.4 Hz), 8.29 (1H, d, J=8.0 Hz), 8.54 (3H, bs).

Example 278

2-[3-(Aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isooquinolinyl]acetamide hydrochloride

(1) To a solution of tert-butyl [4-butoxy-6-(cyanomethyl)-2-neopentyl-1-oxo-1,2-dihydro-3-

isoquinolinyl]methylcarbamate (0.45g, 1 mmol) in ethanol (20 ml) was added a solution of potassium hydroxide (0.40 g, 10 mmol) in water (5 ml). The mixture was refluxed for 10h. The reaction mixture was poured into 5 water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give crude amorphous solid. A solution of the amorphous solid, 1-ethyl-3-(3-
10 dimethylaminopropyl)carbodiimide hydrochloride (0.19 g, 1 mmol) and 1-hydroxybenzotriazole ammonium salt (0.15 g, 1 mmol) in N,N-dimethylformamide (10 ml) was stirred for 2h at room temperature. The resulting reaction mixture was poured into water and extracted with ethyl acetate.
15 The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give tert-butyl [6-(2-amino-2-oxoethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.13 g, 54.2%) as crystals.

Melting point 197-198°C.

¹H-NMR(CDCl₃) δ: 0.99 (9H, s), 1.04 (3H, t, J=7.4 Hz), 1.45 (9H, s), 1.46-1.64 (2H, m), 1.80-1.90 (2H, m), 3.74 (2H, s), 3.87 (2H, t, J=6.5 Hz), 4.14 (2H, bs), 4.57 (2H, d, J=5.4 Hz), 4.71 (1H, bs), 5.47 (1H, bs), 5.54 (1H, bs), 7.40 (1H, dd, J=1.4, 8.0 Hz), 7.60 (1H, d, J=1.4 Hz), 8.38 (1H, d, J=8.0 Hz).
(2) Tert-butyl [6-(2-amino-2-oxoethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (95 mg, 0.2 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The solution was stirred at room temperature for 2h. The reaction was concentrated under 35 reduced pressure, and the residue was crystallized from methanol - diisopropyl ether to give 2-[3-(aminomethyl)-

4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinyl]acetamide hydrochloride (75 mg, 91.5%) as crystals.

Melting point 163-165°C.

5 $^1\text{H-NMR}(\text{DMSO-d}_6)$ δ : 0.90 (9H, s), 1.00 (3H, t, $J=7.5$ Hz), 1.52-1.59 (2H, m), 1.80-1.90 (2H, m), 3.61 (2H, s), 3.93 (2H, s), 4.02 (2H, bs), 4.24 (2H, s), 7.03 (1H, bs), 7.50 (1H, d, $J=8.5$ Hz), 7.67 (1H, s), 7.69 (1H, bs), 8.20 (1H, d, $J=8.5$ Hz).

10 **Example 279**

[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]acetonitrile hydrochloride

(1) To a mixture of tert-butyl [6-(hydroxymethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-

15 isoquinolinyl]methylcarbamate (0.33 g, 0.75 mmol), triethylamine (0.18 mL, 1.1 mmol), N,N,N',N'-tetramethylethylenediamine (0.011 mL, 0.075 mmol), toluene (6 mL) and tetrahydrofuran (6 mL) was added dropwise a solution of methanesulfonyl chloride (0.088 mL, 1.1 mmol) in toluene (4 mL) under ice-cooling. The mixture was stirred under ice-cooling for 30 min, the reaction mixture was poured into 0.1N hydrochloric acid (50 mL) and extracted with ethyl acetate (50 mL). The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give (3-{[(tert-

20 butoxycarbonyl)amino]methyl}-2-isobutyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-6-yl)methyl methanesulfonate (0.39 g, 100 %) as colorless powder.

25

30 $^1\text{H-NMR}$ (CDCl_3) δ : 1.01 (6H, d, $J=7.0$ Hz), 1.43 (9H, s), 2.15-2.30 (1H, m), 2.91 (3H, s), 4.09 (2H, d, $J=7.0$ Hz), 4.22 (2H, d, $J=6.0$ Hz), 4.45 (1H, br), 5.18 (2H, s), 6.93 (1H, d, $J=1.0$ Hz), 7.15-7.30 (2H, m), 7.45-7.60 (4H, m), 8.51 (1H, d, $J=8.6$ Hz).

35 (2) To a mixture of (3-{[(tert-butoxycarbonyl)amino]methyl}-2-isobutyl-1-oxo-4-phenyl-

1,2-dihydroisoquinolin-6-yl)methyl methanesulfonate (0.39 g, 0.75 mmol) in acetonitrile (5 mL) and tetrahydrofuran (4 mL) were added trimethylsilyl cyanide (0.15 mL, 1.1 mmol) and a solution of 1.0 M 5 tetrabutylammonium fluoride in tetrahydrofuran (1.1 mL), and then the mixture was stirred at 80°C for 30 min. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate= 5:2 (v/v)) to give tert-butyl [6-(cyanomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.25 g, 75%) as a colorless oil.

¹H-NMR (CDCl₃) δ: 1.01 (6H, d, J= 6.8 Hz), 1.43 (9H, s), 2.15-2.30 (1H, m), 3.71 (2H, s), 4.09 (2H, d, J= 6.8 Hz), 15 4.21 (2H, d, J= 5.4 Hz), 4.46 (1H, br), 6.86 (1H, d, J= 1.8 Hz), 7.20-7.30 (2H, m), 7.43 (1H, dd, J= 1.8, 8.4 Hz), 7.50-7.60 (3H, m), 8.49 (1H, d, J= 8.4 Hz).

(3) To a solution of tert-butyl [6-(cyanomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.13 g, 0.29 mmol) in ethyl acetate (4 mL) was added a 4N hydrogen chloride ethyl acetate solution (1 mL), and the mixture was stirred at room temperature for 12 h. The reaction was concentrated under reduced pressure, and the residue was 20 crystallized from diisopropyl ether and washed with diisopropyl ether (5 mL X 2) to give [3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]acetonitrile hydrochloride (0.096 g, 88%) as a pale yellow powder.

¹H-NMR (DMSO-d₆) δ: 0.92 (6H, d, J= 6.6 Hz), 1.95-2.20 (1H, m), 3.87 (2H, bs), 4.06 (2H, d, J= 5.4 Hz), 4.13 (2H, s), 6.85-6.95 (1H, m), 7.35-7.45 (3H, m), 7.50-7.65 (3H, m), 8.36 (1H, d, J= 8.0 Hz), 8.43 (3H, bs). Melting point: 142-144°C

35 Example 280
N-[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-

dihydro-6-isoquinolinyl]-N'-methoxyurea hydrochloride
(1) To a solution of 3-{[(tert-butoxycarbonyl)amino]methyl}-2-isobutyl-1-oxo-4-phenyl-1,2-dihydroisoquinoline-6-carboxylic acid (0.15 g, 0.33 mmol) in N,N-dimethylformamide (5 mL) was added diphenylphosphoryl azide (0.09 mL, 0.40 mmol) and triethylamine (0.056 mL, 0.40 mmol), and the mixture was stirred at room temperature for 2 h. The reaction mixture was poured into water (50 mL) and extracted with ethyl acetate (30 mL X 2). The organic layers were combined, washed with water (50 mL) and brine (20 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in toluene (20 mL), and the solution was refluxed for 1 h.
The reaction mixture was allowed to cool to room temperature, and a mixture of O-methylhydroxyamine hydrochloride (0.088 g, 0.40 mmol) and triethylamine (0.056 mL, 0.40 mmol) in N,N-dimethylformamide (2 mL) was added thereto. The resulting reaction mixture was stirred at room temperature for 1 h and then poured into water (100 mL). The organic layer was separated and the aqueous layer was extracted twice with ethyl acetate. The organic layers were combined, washed with 0.1M aqueous citric acid solution (20 mL) and brine (10 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate= 1:1 (v/v)) to give tert-butyl {[(methoxyamino)carbonyl]amino}-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.13 g, 81%) as a colorless oil.

¹H-NMR (CDCl₃) δ: 1.00 (6H, d, J= 6.9 Hz), 1.43 (9H, s), 2.20-2.35 (1H, m), 3.74 (3H, d, J= 0.6 Hz), 4.05 (2H, d, J= 6.9 Hz), 4.19 (2H, d, J= 5.5 Hz), 4.59 (1H, br), 6.95 (1H, bs), 7.22 (1H, br), 7.25-7.30 (3H, m), 7.45-7.70 (4H, m), 8.40 (1H, d, J= 8.7 Hz).

(2) N-[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-N'-methoxyurea hydrochloride (0.049 g, 46%) as a pale yellow powder [synthesized according to the method similar to that in Example 279

5 (3) from tert-butyl (2-isobutyl-6-[(methoxyamino)carbonyl]amino)-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.12 g, 0.25 mmol)]

¹H-NMR (DMSO-d₆) δ: 0.91 (6H, d, J= 6.6 Hz), 2.00-2.20 (1H, m), 3.55 (3H, s), 3.83 (2H, bs), 4.02 (2H, d, J= 6.6 Hz), 7.25 (1H, d, J= 1.8 Hz), 7.30-7.40 (2H, m), 7.50-7.60 (3H, m), 7.82 (1H, dd, J= 1.8, 8.8 Hz), 8.21 (1H, d, J= 8.8 Hz), 8.39 (3H, bs), 9.29 (1H, s), 9.60 (1H, s).

15 Melting point: 297-299°C

Example 281

3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinecarbohydrazide dihydrochloride

20 (1) A mixture of methyl 3-[(tert-butoxycarbonyl)amino]methyl-2-isobutyl-1-oxo-4-phenyl-1,2-dihydroisoquinoline-6-carboxylate (0.12 g, 0.27 mmol) and hydrazine monohydrate (0.65 mL, 13 mmol) in methanol (6 mL) was stirred in a sealed tube at 75°C for 2 h. The reaction mixture was concentrated, and the residue was recrystallized from water - methanol to give

25 tert-butyl [6-(hydrazinocarbonyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.12 g, 96%) as colorless crystals.

¹H-NMR (CDCl₃) δ: 1.00 (6H, d, J= 7.0 Hz), 1.43 (9H, s), 2.20-2.30 (1H, m), 2.48 (3H, br), 4.08 (2H, d, J= 7.0 Hz), 4.20 (2H, d, J= 5.2 Hz), 4.70 (1H, br), 7.20-7.30 (3H, m), 7.45-7.55 (3H, m), 7.69 (1H, d, J= 5.4 Hz), 8.43 (1H, d, J= 8.6 Hz).

30 (2) 3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinecarbohydrazide dihydrochloride (0.095 g, 95%) as a pale yellow powder.

[synthesized according to the method similar to that in Example 279 (3) from tert-butyl [6-(hydrazinocarbonyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.11 g, 0.29 mmol)]

5 ¹H-NMR (DMSO-d₆) δ: 0.93 (6H, d, J= 6.6 Hz), 2.00-2.20 (1H, m), 3.88 (2H, bs), 4.09 (2H, d, J= 7.0 Hz), 7.35-7.45 (3H, m), 7.55-7.65 (3H, m), 8.00 (1H, dm, J= 8.4 Hz), 8.45 (1H, d, J=8.4 Hz), 8.56 (3H, bs), 11.62 (1H, bs).

10 Melting point : 291-292°C

Example 282

3-(Aminomethyl)-2-isobutyl-6-(5-methyl-1,3,4-oxadiazol-2-yl)-4-phenyl-1(2H)-isoquinolinone

(1) A mixture of tert-butyl [6-(hydrazinocarbonyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.23 g, 0.50 mmol) and trimethyl orthoacetate (2.0 mL, 11 mmol) in 1-butanol (10 mL) was refluxed for 20 min. To the reaction mixture was added 1,8-diazabicyclo[5.4.0]-7-undecene (0.075 mL, 0.50 mmol), and then the mixture was refluxed for 1h. The resulting reaction mixture was neutralized with acetic acid (0.040 mL, 0.70 mmol) and concentrated under reduced pressure. The residue was partitioned between water (10 mL) and ethyl acetate (30 mL). The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate= 2:1 (v/v)) to give tert-butyl [2-isobutyl-6-(5-methyl-1,3,4-oxadiazol-2-yl)-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.22 g, 91%) as crystals.

1¹H-NMR (CDCl₃) δ: 1.02 (6H, d, J= 7.2 Hz), 1.43 (9H, s), 2.15-2.35 (1H, m), 2.57 (3H, s), 4.10 (2H, d, J= 7.2 Hz), 4.22 (2H, d, J= 5.4 Hz), 4.57 (1H, br), 7.20-7.35 (2H, m), 7.50-7.65 (4H, m), 8.05 (1H, dm, J= 8.4 Hz), 8.58 (1H, dd, J= 1.4, 8.4 Hz).

(2) A mixture of tert-butyl [2-isobutyl-6-(5-methyl-1,3,4-oxadiazol-2-yl)-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.20 g, 0.41 mmol) and 4N hydrogen chloride ethyl acetate solution (4 mL) was
5 stirred for 17h at room temperature. The reaction mixture was concentrated, the residue was washed with diisopropyl ether (5 mL X 2) to give a pale yellow powder. The powder was added to aqueous saturated sodium hydrogencarbonate (30 mL), the resulting mixture was
10 extracted with ethyl acetate-tetrahydrofuran (1:1, v/v, 50 mL X 2). The organic layers were combined, washed with brine (25 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography
15 (ethyl acetate:methanol= 20:1 (v/v)) and recrystallized from n-hexane-ethyl acetate to give 3-(aminomethyl)-2-isobutyl-6-(5-methyl-1,3,4-oxadiazol-2-yl)-4-phenyl-1(2H)-isoquinolinone (0.11 g, 72%) as pale yellow crystals.
20 ¹H-NMR (CDCl₃) δ: 1.02 (6H, d, J= 6.6 Hz), 2.15-2.40 (1H, m), 2.57 (3H, s), 3.69 (2H, bs), 4.24 (2H, d, J= 7.4 Hz), 7.25-7.35 (2H, m), 7.45-7.60 (3H, m), 7.62 (1H, d, J=1.6 Hz), 8.05 (1H, dd, J= 1.6, 8.4 Hz), 8.59 (1H, d, J=8.4 Hz).

25 Melting point : 179-181°C

Example 283

2-[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]acetamide hydrochloride
(1) A mixture of tert-butyl [6-(cyanomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.13 g, 0.29 mmol), 2N potassium hydroxide solution (5 mL) and ethanol (5 mL) was refluxed for 4 h. The reaction mixture was diluted with 0.1N sodium hydroxide solution (100 mL) and washed
30 with ethyl acetate (20 mL X 2). The aqueous layer was
35 separated, acidified with 1N hydrochloric acid and

extracted with ethyl acetate (100 mL X 2). The organic layers were combined, washed with brine (20 mL), saturated aqueous sodium hydrogencarbonate (50 mL) and brine (50 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give (3-
5 {{(tert-butoxycarbonyl)amino}methyl}-2-isobutyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-6-yl)acetic acid (0.36 g, 87%) as a pale yellow oil.

¹H-NMR (CDCl₃) δ: 0.98 (6H, d, J= 6.6 Hz), 1.42 (9H, s),
10 2.15-2.35 (1H, m), 3.60 (2H, s), 3.95-4.25 (4H, m), 4.48
(1H, br), 6.81 (1H, d, J= 1.2 Hz), 7.10-7.30 (3H, m),
7.38 (1H, d, J= 7.5 Hz), 7.45-7.55 (2H, m), 8.40 (1H, dm,
J= 7.5 Hz).

(2) A mixture of (3-{{(tert-
15 butoxycarbonyl)amino}methyl}-2-isobutyl-1-oxo-4-phenyl-
1,2-dihydroisoquinolin-6-yl)acetic acid (0.15 g, 0.32
mmol), 1-hydroxybenzotriazole ammonium salt (0.074 g,
0.48 mmol) and 1-ethyl-3-(3-
dimethylaminopropyl)carbodiimide hydrochloride (0.093 g,
20 0.48 mmol) in N,N-dimethylformamide (10 mL) was stirred
at room temperature for 17 h. The reaction mixture was
poured into 0.1N aqueous citric acid solution (50 mL)
and extracted with ethyl acetate (25 mL X 2). The
organic layers were combined, washed with 0.1N aqueous
25 citric acid solution (50 mL), saturated aqueous sodium
hydrogencarbonate (50 mL) and brine (50 mL), dried over
anhydrous magnesium sulfate and concentrated under
reduced pressure. The residue was purified by silica gel
column chromatography (ethyl acetate) to give tert-butyl
30 [6-(2-amino-2-oxoethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-
dihydro-3-isoquinolinyl]methylcarbamate (0.12 g, 81%) as
colorless crystals.

¹H-NMR (CDCl₃) δ: 1.00 (6H, d, J= 6.6 Hz), 1.42 (9H, s),
35 2.15-2.30 (1H, m), 3.54 (2H, s), 4.00-4.25 (4H, m), 4.44
(1H, br), 5.31 (2H, br), 6.82 (1H, m), 7.20-7.30 (2H, m),
7.35-7.55 (4H, m), 8.46 (1H, dm, J= 8.0 Hz).

(3) 2-[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]acetamide hydrochloride (0.090 g, 90%) as pale yellow crystals.

[synthesized according to the method similar to that in Example 279 (3) from tert-butyl [6-(2-amino-2-oxoethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.11 g, 0.25 mmol)]
 $^1\text{H-NMR}$ (CD_3OD) δ : 1.00 (6H, d, $J= 6.6$ Hz), 2.10-2.30 (1H, m), 3.52 (2H, s), 4.05-4.20 (4H, m), 7.00 (1H, d, $J= 1.2$ Hz), 7.35-7.45 (2H, m), 7.50-7.65 (5H, m), 8.37 (1H, d, $J= 8.0$ Hz).

Melting point : 231-233°C

Example 284

2-{{[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]methyl}-1H-isoindole-1,3(2H)-dione hydrochloride

(1) To a solution of (3-{{[(tert-butoxycarbonyl)amino]methyl}-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinyl)methyl methanesulfonate (1.1 g, 2.11 mmol) in N,N -dimethylformamide (20 mL) was added potassium phthalimide (0.47 g, 2.5 mmol), and the mixture was stirred at room temperature for 17 h. The reaction mixture was poured into water (200 mL) and extracted with ethyl acetate (100 mL X 2). The organic layers were combined, washed with 0.2N hydrochloric acid (100 mL), saturated aqueous sodium hydrogen carbonate (50 mL) and brine (50 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate= 5:2 (v/v)) to give tert-butyl {6-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl}methylcarbamate (0.99 g, 84%) as colorless crystals.

$^1\text{H-NMR}$ (CDCl_3) δ : 0.98 (6H, d, $J= 6.6$ Hz), 1.42 (9H, s), 2.10-2.30 (1H, m), 4.05 (2H, d, $J= 7.4$ Hz), 4.20 (2H, d,

J= 7.4 Hz), 4.42 (1H, br), 4.80 (2H, s), 6.90 (1H, d, *J*= 1.2 Hz), 7.15-7.25 (2H, m), 7.35-7.45 (4H, m), 7.65-7.75 (2H, m), 7.75-7.85 (2H, m), 8.40 (1H, d, *J*= 8.0 Hz). (2) 2-{[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]methyl}-1H-isoindole-1,3(2H)-dione hydrochloride (0.10 g, 100%) as a colorless powder.

[synthesized according to the method similar to that in Example 279 (3) from tert-butyl {6-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-2-isobutyl-1-oxo-4-

10 phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.11 g, 0.20 mmol)]

¹H-NMR (DMSO-d₆) δ: 0.90 (6H, d, *J*= 6.6 Hz), 1.95-2.20 (1H, m), 3.87 (2H, bs), 4.04 (2H, d, *J*= 5.4 Hz), 4.77 (2H, s), 6.65-6.75 (1H, m), 7.25-7.30 (2H, m), 7.35-7.45 (3H, m), 7.52 (1H, dm, *J*= 8.2 Hz), 7.87 (4H, s), 8.29 (1H, d, *J*= 8.2 Hz), 8.31 (3H, bs).

Melting point: 196-199°C

Example 285

N-{[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-

20 dihydro-6-isoquinolinyl]methyl}acetamide hydrochloride (1) A mixture of tert-butyl {6-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl}methylcarbamate (0.85 g, 1.5 mmol) and hydrazine monohydrate (0.6 mL, 12 mmol) in

25 ethanol (20 mL), and tetrahydrofuran (10 mL) was stirred at room temperature for 17 h. The reaction mixture was filtered, and the filtrate was concentrated. After the residue was dissolved in ethyl acetate (50 mL), the solution was filtrated to remove insoluble material.

30 The filtrate was concentrated to give tert-butyl [6-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.82 g) as a crude pale yellow oil. To a solution of the crude oil (0.16 g) in tetrahydrofuran (2 mL) was added acetic anhydride (0.034

35 mL, 0.36 mmol), and then the mixture was stirred at room temperature for 4 h. The reaction mixture was washed

- with water (4 mL) and concentrated. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate= 4:1 (v/v)) to give tert-butyl {6-[(acetylamino)methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl}methylcarbamate (0.090 g, 63%) as a pale yellow solid.
- 5 ¹H-NMR (CDCl₃) δ: 1.00 (6H, d, J= 6.6 Hz), 1.43 (9H, s), 1.96 (3H, s), 2.25-2.35 (1H, m), 4.06 (2H, d, J= 7.6 Hz), 4.19 (2H, d, J= 5.4 Hz), 4.38 (2H, d, J= 6.6 Hz), 4.59 (1H, br), 5.84 (1H, br), 6.76 (1H, m), 7.20-7.55 (6H, m), 8.38 (1H, dm, J= 8.4 Hz).
- 10 (2) N-{[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]methyl}acetamide hydrochloride (0.068 g, 96%) as a pale yellow powder.
- 15 [synthesized according to the method similar to that in Example 279 (3) from tert-butyl {6-[(acetylamino)methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl}methylcarbamate (0.082 g, 0.17 mmol)]
- 20 ¹H-NMR (DMSO-d₆) δ: 0.91 (6H, d, J= 6.6 Hz), 1.75 (3H, s), 1.95-2.20 (1H, m), 3.87 (2H, bs), 4.04 (2H, d, J= 6.6 Hz), 4.20 (2H, d, J= 6.6 Hz), 6.73 (1H, s), 7.30-7.40 (2H, m), 7.44 (1H, dd, J= 1.6, 8.4 Hz), 7.50-7.60 (3H, m), 8.28 (1H, d, J= 8.4 Hz), 8.30-8.45 (4H, m).
- 25 Melting point : 134-139°C
- Example 286**
- N-{[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]methyl}-2-methylpropanamide hydrochloride
- 30 (1) To a solution of crude tert-butyl [6-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.16 g) (Example 285) in tetrahydrofuran (2 mL) was added isobutyryl chloride (0.038 mL, 0.36 mmol) and triethylamine (0.050 mL, 0.36 mmol), and the mixture was stirred at room temperature for 4 h. The reaction mixture was washed with water (4
- 35

mL) and concentrated. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate= 4:1 (v/v)) to give tert-butyl {2-isobutyl-6-[(isobutyryl amino)methyl]-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl}methylcarbamate (0.11 g, 75%) as a pale yellow solid.

1H-NMR (CDCl₃) δ: 0.99 (6H, d, J= 6.6 Hz), 1.07 (6H, d, J= 7.0 Hz), 1.43 (9H, s), 2.15-2.35 (2H, m), 4.06 (2H, d, J= 7.2 Hz), 4.20 (2H, d, J= 5.4 Hz), 4.41 (2H, d, J= 6.2 Hz), 4.58 (1H, br), 5.79 (1H, br), 6.77 (1H, d, J= 1.2 Hz), 7.20-7.60 (6H, m), 8.38 (1H, dm, J= 8.2 Hz).

(2) N-{[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]methyl}-2-methylpropanamide hydrochloride (0.091 g, 98%) as a pale yellow powder.

15 [synthesized according to the method similar to that in Example 279 (3) from tert-butyl {2-isobutyl-6-[(isobutyryl amino)methyl]-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl}methylcarbamate (0.11 g; 0.21 mmol)].

1H-NMR (DMSO-d₆) δ: 0.86 (6H, d, J= 6.6 Hz), 0.91 (6H, d, J= 6.6 Hz), 1.95-2.35 (2H, m), 3.84 (2H, bs), 4.06 (2H, d, J= 7.0 Hz), 4.24 (2H, d, J= 5.8 Hz), 6.75 (1H, s), 7.30-7.40 (2H, m), 7.43 (1H, dd, J= 1.0; 8.4 Hz), 7.45-7.60 (3H, m), 8.27 (1H, bs), 8.27 (1H, d, J= 8.4 Hz), 8.52 (3H, bs).

25 Melting point: 189-191°C

Example 287

Ethyl [3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]methylcarbamate hydrochloride

(1) To a solution of crude tert-butyl [6-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.16 g) (Example 285) in tetrahydrofuran (2 mL) were added ethyl chloroformate (0.035 mL, 0.36 mmol) and triethylamine (0.050 mL, 0.36 mmol), and the mixture was stirred at room temperature 35 for 4 h. The reaction mixture was washed with water (4 mL) and concentrated. The residue was purified by silica

gel column chromatography (n-hexane:ethyl acetate= 4:1 (v/v)) to give ethyl [3-{{(tert-butoxycarbonyl)amino}methyl}-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl)methylcarbamate (0.13 g, 5 87%) as pale yellow powder.

¹H-NMR (CDCl₃) δ: 1.00 (6H, d, J= 6.6 Hz), 1.21 (3H, t, J= 7.0 Hz), 1.42 (9H, s), 2.15-2.35 (1H, m), 4.07 (2H, d, J= 7.8 Hz), 4.09 (2H, q, J= 7.0 Hz), 4.19 (2H, d, J= 7.4 Hz), 4.31 (2H, d, J= 6.6 Hz), 4.49 (1H, br), 4.96 (1H, br), 6.79 (1H, s); 7.20-7.55 (6H, m), 8.42 (1H, d, J= 8.4 Hz).

(2) Ethyl [3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl)methylcarbamate hydrochloride (0.092 g, 88%) as a colorless powder.

15 [synthesized according to the method similar to that in Example 279 (3) from ethyl [3-{{(tert-butoxycarbonyl)amino}methyl}-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl)methylcarbamate (0.12 g, 0.24 mmol)]

20 ¹H-NMR (DMSO-d₆) δ: 0.91 (6H, d, J= 6.6 Hz), 1.11 (3H, t, J= 7.4 Hz), 2.00-2.20 (1H, m), 3.86 (2H, bs), 3.91 (2H, q, J= 7.4 Hz), 4.07 (2H, d, J= 7.8 Hz), 4.13 (2H, d, J= 6.0 Hz), 6.77 (1H, s), 7.30-7.40 (2H, m), 7.45 (1H, dd, J= 1.6, 8.2 Hz), 7.50-7.60 (3H, m), 7.64 (1H, d, J= 6.0 Hz), 8.28 (1H, d, J= 8.2 Hz), 8.55 (3H, bs).

Melting point: 184-187°C

Example 288

N-{{[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl)methyl}methanesulfonamide 30 hydrochloride

(1) To a solution of crude tert-butyl [6-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.16 g) (Example 285) in tetrahydrofuran (2 mL) was added methanesulfonyl chloride (0.028 mL, 0.36 mmol) and triethylamine (0.050 mL, 0.36 mmol), and the mixture was stirred at room

temperature for 4 h. The reaction mixture was washed with water (4 mL) and concentrated. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate= 2:1 (v/v)) to give tert-butyl (2-isobutyl-6-[(methylsulfonyl)amino]methyl)-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.13 g, 84%) as a pale yellow oil.

¹H-NMR (CDCl₃) δ: 1.00 (6H, d, J= 6.6 Hz), 1.43 (9H, s), 2.15-2.35 (1H, m), 2.80 (3H, s), 4.07 (2H, d, J= 7.2 Hz), 4.20 (2H, d, J= 5.8 Hz), 4.29 (2H, d, J= 6.6 Hz), 4.52 (1H, br), 4.71 (1H, bt, J= 5.8 Hz), 6.86 (1H, d, J= 1.2 Hz), 7.20-7.30 (2H, m), 7.44 (1H, dd, J= 1.6 8.0 Hz), 7.45-7.60 (3H, m), 8.44 (1H, d, J= 8.0 Hz).

(2) N-[(3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl)methyl]methanesulfonamide hydrochloride (0.097 g, 100%) as a pale yellow powder. [synthesized according to the method similar to that in Example 279 (3) from tert-butyl (2-isobutyl-6-[(methylsulfonyl)amino]methyl)-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.11 g, 0.21 mmol)]

¹H-NMR (DMSO-d₆) δ: 0.91 (6H, d, J= 6.6 Hz), 1.95-2.20 (1H, m), 2.80 (3H, s), 3.86 (2H, bs), 4.07 (2H, d, J= 7.0 Hz), 4.14 (2H, d, J= 6.2 Hz), 6.88 (1H, s), 7.35-7.45 (2H, m), 7.50-7.65 (4H, m), 7.63 (1H, t, J= 6.2 Hz), 8.32 (1H, d, J= 8.0 Hz), 8.55 (3H, bs).

Melting point: 117-120°C

Example 289

3,6-Bis(aminomethyl)-2-isobutyl-4-phenyl-1(2H)-isoquinolinone dihydrochloride

(1) To a solution of crude tert-butyl [6-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.16 g)(Example 286) in tetrahydrofuran (2 mL) was added di-t-butyl dicarbonate (0.086 mL, 0.36 mmol), and the mixture was stirred at room temperature for 4 h. The reaction mixture was

washed with water (4 mL) and concentrated. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate= 4:1 (v/v)) to give tert-butyl (3-{{(tert-butoxycarbonyl)amino}methyl}-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isouquinolinyl)methylcarbamate (0.14 g, 93%) as a colorless powder.

5 $^1\text{H-NMR}$ (CDCl_3) δ : 1.00 (6H, d, $J= 6.6$ Hz), 1.39 (9H, s), 1.42 (9H, s), 2.15-2.35 (1H, m), 4.07 (2H, d, $J= 7.4$ Hz), 4.19 (2H, d, $J= 6.6$ Hz), 4.26 (2H, d, $J= 6.6$ Hz), 4.45 (1H, br), 4.81 (1H, br), 6.81 (1H, d, $J= 1.1$ Hz), 7.20-7.30 (2H, m), 7.30-7.40 (1H, m), 7.45-7.55 (3H, m), 8.42 (1H, d, $J= 8.0$ Hz).

10 (2) 3,6-Bis(aminomethyl)-2-isobutyl-4-phenyl-1(2H)-isoquinolinone dihydrochloride (0.080 g, 76%) as colorless powder. [synthesized according to the method similar to that in Example 279 (3) from tert-butyl (3-{{(tert-butoxycarbonyl)amino}methyl}-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isouquinolinyl)methylcarbamate (0.14 g, 0.26 mmol)]

15 $^1\text{H-NMR}$ (DMSO-d_6) δ : 0.91 (6H, d, $J= 6.6$ Hz), 1.95-2.20 (1H, m), 3.85 (2H, bs), 4.01 (2H, bs), 4.10 (2H, d, $J= 6.6$ Hz), 7.02 (1H, d, $J= 1.0$ Hz), 7.35-7.45 (2H, m), 7.50-7.60 (3H, m), 7.72 (1H, dm, $J= 8.4$ Hz), 8.36 (1H, d, $J= 8.4$ Hz), 8.45 (3H, bs), 8.62 (3H, bs).

20 Melting point : 282-285°C

Example 290

3-(Aminomethyl)-2-isobutyl-4-phenyl-6-[5-(trifluoromethyl)-1H-1,2,4-triazol-3-yl]-1(2H)-isoquinolinone dihydrochloride

25 (1) A mixture of ethyl trifluoroacetate (0.038 mL, 0.31 mmol) and hydrazine monohydrate (0.026 mL, 0.50 mmol) in tetrahydrofuran (3 mL) was refluxed in a sealed tube for 1 h, the reaction was allowed to cool to room temperature. To the mixture were added tert-butyl {6-

30 [amino(imino)methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isouquinolinyl)methylcarbamate diacetate (0.14

g, 0.25 mmol) and sodium hydroxide (0.027 g, 0.55 mmol), and the resulting mixture was refluxed for 3 h. The reaction mixture was partitioned between water (10 mL) and ethyl acetate (30 mL). The organic layer was washed 5 with water and brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate= 3:1 (v/v)) to give tert-butyl {2-isobutyl-1-oxo-4-phenyl-6-[5-(trifluoromethyl)-1H- 10 1,2,4-triazol-3-yl]-1,2-dihydro-3- isoquinolinyl}methylcarbamate (0.074 g, 55%) as a colorless powder.

¹H-NMR (CDCl₃) δ: 1.00 (6H, d, J= 6.6 Hz), 1.43 (9H, s), 2.10-2.35 (1H, m), 4.08 (2H, d, J= 7.4 Hz), 4.18 (2H, d, 15 J= 5.2 Hz), 4.71 (1H, br), 7.20-7.30 (3H, m), 7.35-7.50 (4H, m), 8.02 (1H, dd, J= 1.6, 8.6 Hz); 8.46 (1H, d, J= 8.6 Hz).

(2) 3-(Aminomethyl)-2-isobutyl-4-phenyl-6-[5-(trifluoromethyl)-1H-1,2,4-triazol-3-yl]-1(2H)- 20 isoquinolinone dihydrochloride (0.063 g, 100%) as yellow crystals.

[synthesized according to the method similar to that in Example 279 (3) from tert-butyl {2-isobutyl-1-oxo-4-phenyl-6-[5-(trifluoromethyl)-1H-1,2,4-triazol-3-yl]- 25 1,2-dihydro-3-isoquinolinyl}methylcarbamate (0.065 g, 0.12 mmol)]

¹H-NMR (DMSO-d₆) δ: 0.94 (6H, d, J= 6.6 Hz), 1.72 (1H, br), 2.05-2.20 (1H, m), 3.88 (2H, bs), 4.09 (2H, d, J= 7.2 Hz), 7.40-7.50 (2H, m), 7.55-7.70 (4H, m), 8.23 (1H, 30 dd, J= 1.6, 8.4 Hz), 8.50 (3H, bs), 8.52 (1H, d, J= 8.4 Hz).

Melting point: 140-143°C

Example 291

3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6- 35 isoquinolinecarboxamidine dihydrochloride

This compound was synthesized according to the method

similar to that in Example 279 (3) from tert-butyl {6-[amino(imino)methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl}methylcarbamate diacetate.

¹H-NMR (DMSO-d₆) δ: 0.92 (6H, d, J= 6.6 Hz), 2.00-2.20 (1H, m), 3.90 (2H, bs), 4.12 (2H, d, J= 7.0 Hz), 7.24 (1H, d, J= 1.6 Hz), 7.40-7.50 (2H, m), 7.50-7.65 (3H, m), 7.86 (1H, dd, J= 1.6, 8.4 Hz), 8.49 (1H, d, J= 8.4 Hz), 8.69 (3H, bs), 9.26 (2H, bs), 9.52 (2H, bs).

Melting point: 171-173°C

10 **Example 292**

Methyl 2-[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-1H-imidazole-4-carboxylate dihydrochloride

(1) To a mixture of tert-butyl {6-[amino(hydroxyimino)-methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl}methylcarbamate (0.47 g, 1.0 mmol), and triethylamine (0.17 mL, 1.2 mmol) in ethyl acetate (10 mL) was added methylpropionate (0.10 g, 1.2 mmol), and the mixture was stirred at room temperature for 17 h.

20 The reaction mixture was poured into water (5 mL), and the organic layer was separated. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. To the residue was added p-xylene (10 mL), the mixture was refluxed for 40 h. The 25 reaction mixture was diluted with ethyl acetate (100 mL), and the solution was washed with water, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate= 1:1

30 (v/v)) to give methyl 2-(3-{[(tert-butoxycarbonyl)amino]methyl}-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl)-1H-imidazole-4-carboxylate (0.22 g, 42%) as an orange powder.

¹H-NMR (CDCl₃) δ: 0.98 (6H, d, J= 6.6 Hz), 1.53 (9H, s), 2.00-2.25 (1H, m), 3.87 (3H, s), 4.00-4.25 (4H, m), 6.37 (1H, br), 7.15-7.25 (1H, m), 7.25-7.55 (7H, m), 7.82 (1H,

dm, $J = 8.4$ Hz), 8.23 (1H, d, $J = 8.4$ Hz).
(2) A solution of methyl 2-(3-{[(tert-butoxycarbonyl)amino]methyl}-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl)-1H-imidazole-4-carboxylate
5 (0.10 g, 0.19 mmol) in trifluoroacetic acid (3 mL) was stirred at room temperature for 5 min. The reaction mixture was concentrated, and purified by HPLC. The desired fractions were concentrated and then to the residue was added a 4N hydrogen chloride ethyl acetate
10 solution (1 mL). The mixture was concentrated, and the residue was recrystallized from ethanol-ethyl acetate (10:1, v/v, 2 mL) to give methyl 2-[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-1H-imidazole-4-carboxylate dihydrochloride (0.050g, 53%) as
15 a yellow powder.

$^1\text{H-NMR}$ (DMSO- d_6) δ : 0.93 (6H, d, $J = 6.6$ Hz), 2.00-2.25 (1H, m), 3.77 (3H, s), 3.84 (2H, s), 4.08 (2H, d, $J = 7.2$ Hz), 7.40-7.50 (3H, m), 7.55-7.65 (4H, m), 7.90 (1H, s), 8.20 (1H, dd, $J = 1.8, 8.4$ Hz), 8.43 (1H, d, $J = 8.4$ Hz),
20 8.51 (3H, bs).

Melting point : 266-270°C

Example 293

Ethyl 3-[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-1,2,4-oxadiazole-5-carboxylate
25 hydrochloride

(1) To a mixture of tert-butyl {6-[amino(hydroxyimino)methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl}methylcarbamate (0.23 g, 0.50 mmol) and pyridine (0.043 mL, 0.53 mmol) in toluene (20 mL) was added ethyl chlorooxacetate (0.059 mL, 0.53 mmol), and the mixture was stirred at room temperature for 1 h and at 80°C for 1 h. The reaction mixture was partitioned between water (50 mL) and ethyl acetate (50 mL). The organic layer was washed with brine, dried over
30 anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel
35

column chromatography (n-hexane:ethyl acetate= 20:1 - 1:3 (v/v)) and recrystallized from diisopropyl ether-ethyl acetate (20:1, v/v, 5 mL) to give ethyl 3-(3-{{(tert-butoxycarbonyl)amino}methyl}-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl)-1,2,4-oxadiazole-5-carboxylate (0.13 g, 48%) as colorless crystals.

¹H-NMR (CDCl₃) δ: 1.02 (6H, d, J= 6.6 Hz), 1.43 (9H, s), 1.47 (3H, t, J= 7.2 Hz), 2.15-2.35 (1H, m), 4.11 (2H, d, J= 7.2 Hz), 4.22 (2H, d, J= 5.6 Hz), 4.45-4.60 (1H, br), 4.54 (2H, q, J= 7.2 Hz), 7.25-7.35 (2H, m), 7.50-7.60 (3H, m), 7.74 (1H, d, J= 1.2 Hz), 8.17 (1H, dd, J= 1.2, 8.4 Hz), 8.60 (1H, d, J= 8.4 Hz).

(2) A solution of ethyl 3-(3-{{(tert-butoxycarbonyl)amino}methyl}-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl)-1,2,4-oxadiazole-5-carboxylate (0.070 g, 0.13 mmol) in trifluoroacetic acid (3 mL) was stirred at room temperature for 5 min. The reaction mixture was concentrated, and to the residue was added a solution of 4N hydrogen chloride in ethyl acetate (3 mL). The mixture was concentrated, and the residue was recrystallized from diisopropyl ether-ethyl acetate-methanol (15:40:1, v/v, 5 mL) to give ethyl 3-[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-1,2,4-oxadiazole-5-carboxylate hydrochloride (0.061 g, 100%) as a colorless powder.

¹H-NMR (DMSO-d₆) δ: 0.94 (6H, d, J= 6.6 Hz), 1.34 (3H, t, J= 7.2 Hz), 2.00-2.20 (1H, m), 3.90 (2H, bs), 4.10 (2H, d, J= 5.0 Hz), 4.43 (2H, d, J= 7.2 Hz), 7.40-7.50 (2H, m), 7.55-7.70 (4H, m), 8.22 (1H, dd, J= 1.4, 8.4 Hz); 8.30-8.60 (3H, br), 8.55 (1H, d, J= 8.4 Hz).

Melting point: 266-270°C

Reference Example 1

2-Benzoyl-4-bromobenzoic acid

A mixture of benzene (2.94 ml), o-dichlorobenzene (20 ml) and aluminum chloride (5.87 g) was cooled to 5°C and 5-bromophthalic anhydride (5.0 g) was added by small

portions while maintaining the temperature of the mixture below 10°C. The mixture was stirred at around 25°C for 1 h and then at 80°C for 1 h. The reaction mixture was cooled to around 5°C and ethyl acetate (40 ml) was added dropwise. Water (20 ml) was added dropwise below 40°C. The organic layer was separated and 4N hydrochloric acid (20 ml) was added. The mixture was stirred until the precipitated solid was dissolved. The organic layer was separated and washed with water (20 ml). The solvent was evaporated and toluene (30 ml) and ethyl acetate (3 ml) were added to the residue, which was followed by heating to 80°C. The obtained solution was cooled to 25°C over 30 min and the precipitated crystals were collected by filtration. The crystals were dissolved in a mixture of toluene (30 ml) and ethyl acetate (1.5 ml) by heating and the obtained solution was cooled to 25°C and then to 5°C. The precipitated crystals were collected by filtration and washed with toluene to give the title compound (2.81 g, yield 41.8%).

²⁰ $^1\text{H-NMR}$ (300MHz, CDCl_3) δ : 7.41-7.46(2H, m), 7.51-7.60(2H, m), 7.69-7.72(3H, m), 7.94(1H, d, $J=8.4\text{Hz}$)

Reference Example 2

Isobutylaminoacetonitrile

To a mixture of isobutylamine (180.3 g),
²⁵ triethylamine (274.9 g) and ethyl acetate (900 ml) was added dropwise bromoacetonitrile (304.8 g) under ice-cooling below 30°C over about 2 h. The reaction mixture was adjusted to 25°C, stirred for 3 h and washed with water (900 ml) and 10% brine (900 ml). The solvent was
³⁰ evaporated and the obtained pale-yellow oil was distilled under reduced pressure. The $\text{bp}_{10\text{mmHg}}$ 82°C fractions were collected to give the title compound (198.3 g).

³⁵ $^1\text{H-NMR}$ (CDCl_3) δ : 0.94(6H, d, $J=6.6\text{Hz}$), 1.17(1H, br), 1.74(1H, m), 2.54(2H, d, $J=6.6\text{Hz}$), 3.59(2H, s)

Experimental Example 1**1) Preparation of dipeptidyl peptidase IV crude enzyme solution**

The enzyme activity of dipeptidyl peptidase IV present in human colonic adenocarcinoma-derived cell line Caco-2 cell membrane has been already reported by Yong S. Chung et al. (Cancer Reserch, vol. 45, pp. 2976-2982, 1985).

A dipeptidyl peptidase IV crude enzyme solution was prepared from culture cell of Caco-2 (ATCC HTB-37). The Caco-2 cells were cultured in D-MEM medium (manufactured by Nissui Pharmaceutical Co., Ltd.) containing 10% FBS (fetal calf serum (manufactured by GIBCO)). The cell extract was prepared by soaking the cells collected by removing the medium in 20 mM phosphate buffer. (pH 7.5) containing 0.5% Triton X-100, extracting for 30 min in an ice bath and separating the supernatant obtained by centrifugation at 1500 g for 30 min. The cell extract (22 ml) was applied to a column of Sephadex G-200 (600 ml, manufactured by Pharmacia Corporation) equilibrated with 20 mM Tris-hydrochloride buffer (pH 7.5) and eluted with the same buffer. The elution was fractionated by 10 ml, examined for enzyme activity and 190 ml-280 ml fractions (90 ml) were collected. The same buffer (260 ml) was added for dilution to give a crude enzyme solution (14 mU/ml, 350 ml). One unit of the dipeptidyl peptidase IV enzyme activity was defined as an enzyme amount that produces 1 μ mol of p-nitroaniline from glycylprolyl-p-nitroanilide in 1 min.

2) Determination of Caco-2-derived dipeptidyl peptidase IV inhibitory activity

The reaction was carried out according to the method of Nagatsu et al. (Analytical Biochemistry, vol. 74, pp. 466-467, 1976) using a 96 well flat-bottomed plate at 37°C.

An N,N-dimethylformamide solution (5 μ l) containing

the test compound was added to a mixture of water (25 µl), 1M Tris-hydrochloride buffer (10 µl, pH 7.5) and 1 mM aqueous glycylprolyl-p-nitroanilide (Gly-Pro-p-NA; manufactured by Bachem AG) solution (50 µl) to prepare a
 5 mixed solution. The Caco-2-derived dipeptidyl peptidase IV crude enzyme solution (10 µl) obtained in the aforementioned 1) was added to the above-mentioned mixed solution and the enzyme reaction was started at 37°C. The absorbance after 0 h and 3 h was measured using a
 10 microplate reader (Multiskan Bichromatic; manufactured by Labsystems) at a wavelength of 405 nm and an increase (ΔOD_s) was determined. At the same time, an increase (ΔOD_c) in absorbance of the reaction mixture without the test compound, and an increase (ΔOD_b) in absorbance of
 15 the reaction mixture without the test compound and the enzyme were determined and percent inhibition of dipeptidyl peptidase IV enzyme activity was calculated from the following formula:

$$\{1 - [(\Delta OD_s - \Delta OD_b) / (\Delta OD_c - \Delta OD_b)]\} \times 100$$

20

The dipeptidyl peptidase IV inhibitory activity of the test compound group is expressed in IC₅₀ value (µM) and shown in Table 8.

25

Table 8

Test compound (Example No.)	IC ₅₀ value (µM)
95	0.28
109	0.36
112	0.25

As shown above, the compound of the present invention has a superior dipeptidyl peptidase IV enzyme
 30 activity, and is useful as an agent for the prophylaxis or treatment of diabetes and the like.

Experimental Example 2**Determination of dipeptidyl peptidase IV inhibitory activity in rat plasma**

The reaction was carried out according to the 5 method of Raymond et al. (Diabetes, vol. 47, pp. 1253-1258, 1998) using a 96 well flat-bottomed plate at 30°C. An N,N-dimethylformamide solution (1 µl) containing the test compound was added to a mixture of water (69 µl), 1M Tris-hydrochloride buffer (10 µl, pH 7.5) and 1 mM 10 aqueous Gly-Pro-p-NA solution (100 µl) to prepare a mixed solution. Plasma (20 µl) prepared from blood of SD rat by a conventional method was added the above-mentioned mixed solution and the enzyme reaction was started at 30°C. The absorbance after 0 h and 1 h was 15 measured using a microplate reader at a wavelength of 405 nm and an increase (ΔODs) was determined. At the same time, an increase (ΔODc) in absorbance of the reaction mixture without the test compound, and an increase (ΔODb) in absorbance of the reaction mixture 20 without the test compound and the enzyme were determined and percent inhibition of dipeptidyl peptidase IV enzyme activity was calculated from the following formula:

$$\{1 - [(\Delta\text{ODs} - \Delta\text{ODb}) / (\Delta\text{ODc} - \Delta\text{ODb})]\} \times 100$$

25 The dipeptidyl peptidase IV inhibitory activity of the test compound group is expressed in IC₅₀ value (µM) and shown in Table 9.

Table 9

Test compound (Example No.)	IC ₅₀ value (µM)
95	0.18
109	0.15
112	0.32

30

As shown above, the compound of the present invention has a superior dipeptidyl peptidase IV enzyme

activity, and is useful as an agent for the prophylaxis or treatment of diabetes and the like.

Experimental Example 3

Plasma glucose-lowering effect and insulinotropic effect
5 in rat.

Female Wistar fatty rats (17-week-old, 6 per group) were fasted overnight and blood was drawn from the tail vein. The plasma glucose level before administration of the test compound was measured. Then the test compound
10 (3 mg/kg body weight/5 mL) suspended in 0.5% methyl cellulose was orally administered to the rats using a gastric tube. Oral glucose tolerance test (1 g/kg body weight/5 mL) was started 60 min later. Blood was drawn at 30 min after starting glucose load, and plasma
15 glucose level and insulin level of the serum were measured. The plasma glucose level was measured using an automatic analyzer (HITACHI 7070) and the insulin level was measured using a radio immunoassay kit (trademark: SHIONORIA insulin kit (manufactured by
20 Shionogi & Co., Ltd.)).

The plasma glucose level and insulin level of the test compound group are expressed in a value (%) relative to the control group and shown in Table 10.

25

Table 10

Test compound (Example No.)	Plasma glucose level (% of control)	insulin level (% of control)
95	82	188
109	73	205
112	76	255

As shown above, the compound of the present invention has a superior plasma glucose level-lowering
30 effect and a superior insulinotropic effect, and is useful as an agent for the prophylaxis or treatment of diabetes and the like.

Formulation Example 1 (production of capsule)

1) compound of Example 95	30 mg
2) fine cellulose powder	10 mg
3) lactose	19 mg
5) <u>4) magnesium stearate</u>	<u>1 mg</u>
total	60 mg

1), 2), 3) and 4) are mixed and filled in gelatin capsules.

Formulation Example 2 (production of tablet)

10) 1) compound of Example 95	30 g
2) lactose	50 g
3) corn starch	15 g
4) calcium carboxymethylcellulose	44 g
5) <u>magnesium stearate</u>	<u>1 g</u>

15) total of 1000 tablets 140 g

The entire amounts of 1), 2) and 3), and 30 g of 4) are kneaded with water, dried in vacuo and granulated.

The granules are mixed with 14 g of 4) and 1 g of 5) and the mixture is compressed with a tabletting machine,

20) whereby 1000 tablets containing 30 mg of compound of Example 95 per tablet are obtained.

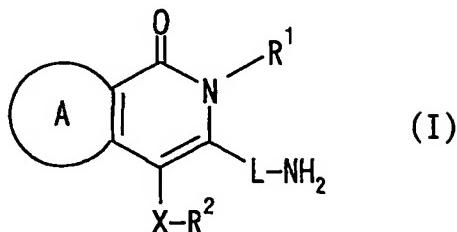
The compound and the pharmaceutical agent of the present invention show a superior peptidase (preferably dipeptidyl peptidase-IV)-inhibitory activity and are

25) useful as an agent for the prophylaxis or treatment of diabetes and the like.

This application is based on patent application Nos. 2001-27349, 2001-292388 and 2001-382232 filed in Japan, the contents of which are hereby incorporated by 30) reference. All of the references cited herein, including patents, patent applications and publications, are hereby incorporated in their entireties by reference.

CLAIMS

1. A compound of the formula



5 wherein

ring A is an optionally substituted 5 to 10-membered aromatic ring;

R¹ and R² are the same or different and each is an optionally substituted hydrocarbon group or 10 an optionally substituted heterocyclic group;

X is a bond, -O-, -S-, -SO-, -SO₂- or -NR³- (R³ is a hydrogen atom or an optionally substituted hydrocarbon group); and

15 L is a divalent hydrocarbon group or a salt thereof, except 3-(aminomethyl)-2,6,7-trimethyl-4-phenyl-1(2H)-isoquinolinone, 3-(aminomethyl)-2-methyl-4-phenyl-1(2H)-isoquinolinone, 3-(aminomethyl)-6-chloro-2-methyl-4-phenyl-1(2H)-20 isoquinolinone and 3-(aminomethyl)-2-isopropyl-4-phenyl-1(2H)-isoquinolinone.

2. The compound of claim 1, wherein the 5 to 10-membered aromatic ring for ring A is a benzene ring.

25 3. The compound of claim 1, wherein the ring A is a 5 to 10-membered aromatic ring optionally having 1 to 3 substituent(s) selected from
 a) a halogen atom,
 30 b) a nitro group,

- c) a cyano group,
- d) a C₁₋₃ alkylenedioxy group,
- e) a C₁₋₁₀ alkyl group or a C₂₋₁₀ alkenyl group, each optionally having 1 to 3 substituent(s) selected from a
- 5 s halogen atom, a hydroxy group, a carboxyl group, an alkoxy carbonyl group having 2 to 8 carbon atoms, a carbamoyl group, a cyano group, an amino group, an alkanoylamino group having 2 to 8 carbon atoms, an alkoxy carbonylamino group having 2 to 8 carbon atoms, an
- 10 alkylsulfonylamino group having 1 to 8 carbon atoms,
- f) an optionally substituted hydroxy group,
- g) an acyl group,
- h) an optionally substituted amino group,
- i) an aryl group having 6 to 14 carbon atoms,
- 15 j) an optionally substituted thiol group, and
- k) an optionally substituted heterocyclic group.

4. The compound of claim 1, wherein R¹ is an alkyl group having 1 to 10 carbon atom(s).

20

5. The compound of claim 1, wherein R¹ is an alkyl group having 4 to 10 carbon atoms.

6. The compound of claim 1, wherein X is a bond or -O-.

25

7. The compound of claim 1, wherein the divalent hydrocarbon group for L is an alkylene group having 1 to 10 carbon atom(s).

30

8. The compound of claim 1, wherein R² is an optionally substituted hydrocarbon group.

9. The compound of claim 1, wherein R² is an alkyl group having 1 to 10 carbon atom(s), an aryl group having 6 to

35

14 carbon atoms or an aralkyl group having 7 to 13 carbon atoms, each optionally having 1 to 3

substituent(s) selected from halogen atom, hydroxy group, nitro group, amino group, optionally halogenated alkyl group having 1 to 6 carbon atom(s), alkoxy group having 1 to 6 carbon atom(s), aromatic heterocyclic group and 5 cycloalkyl group having 3 to 10 carbon atoms.

10. The compound of claim 1, which is 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-1,3-thiazole-4-carbonitrile,
 - 15 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-1,3-thiazole-4-carboxylic acid, 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-1,3-thiazole-4-carboxamide, ethyl 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-20 dihydro-6-isoquinolyl]-1,3-thiazole-4-carboxylate, (E)-3-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-2-propenamide, (E)-3-[3-(aminomethyl)-2-isobutyl-4-phenyl-1-oxo-1,2-dihydro-6-isoquinolyl]-2-propenamide,
 - 25 3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinecarboxamide, 2-[[3-(aminomethyl)-2-isobutyl-4-phenyl-1-oxo-1,2-dihydro-6-isoquinolyl]oxy]acetamide, or a salt thereof.
- 25
11. A crystal of 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-1,3-thiazole-4-carbonitrile or a salt thereof.
 - 30 12. A crystal of 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-1,3-thiazole-4-carboxamide or a salt thereof.
 - 35 13. A crystal of 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-1,3-thiazole-4-carboxamide or a salt thereof.

14. A crystal of ethyl 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-1,3-thiazole-4-carboxylate or a salt thereof.

5

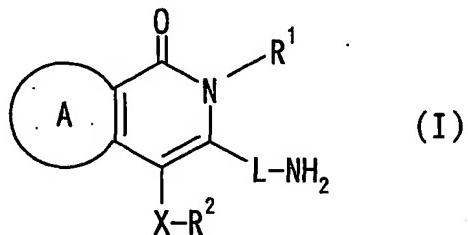
15. A crystal of (E)-3-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-2-propenamide or a salt thereof.

10 16. A crystal of (E)-3-[3-(aminomethyl)-2-isobutyl-4-phenyl-1-oxo-1,2-dihydro-6-isoquinolyl]-2-propenamide or a salt thereof.

17. A crystal of 3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinecarboxamide or a salt thereof.

18. A crystal of 2-[[3-(aminomethyl)-2-isobutyl-4-phenyl-1-oxo-1,2-dihydro-6-isoquinolyl]oxy]acetamide or a salt thereof.

19. A pharmaceutical agent containing a compound of the formula .



25 wherein

ring A is an optionally substituted 5 to 10-membered aromatic ring;

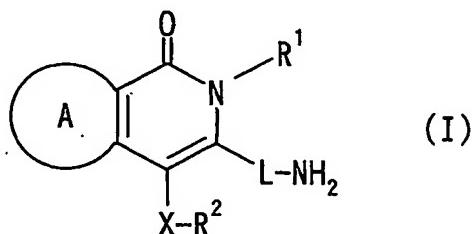
R¹ and R² are the same or different and each is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic

30

X . group;
 X is a bond, -O-, -S-, -SO-, -SO₂- or -NR³-
 (R³ is a hydrogen atom or an optionally
 substituted hydrocarbon group); and
 5 L is a divalent hydrocarbon group,
 or a salt thereof.

20. A pharmaceutical agent comprising the pharmaceutical agent of claim 19 in combination with at least one
 10 member selected from an insulin preparation, an insulin sensitizer, an α-glucosidase inhibitor, a biguanide and an insulin secretagogue.

21. An agent for prophylaxis or treatment of diabetes,
 15 which contains a compound of the formula



wherein

ring A is an optionally substituted 5 to 10-membered aromatic ring;

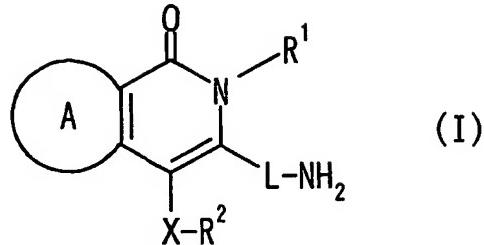
20 R¹ and R² are the same or different and each is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;

X is a bond, -O-, -S-, -SO-, -SO₂- or -NR³-
 25 (R³ is a hydrogen atom or an optionally substituted hydrocarbon group); and

L is a divalent hydrocarbon group,
 a salt thereof or a prodrug thereof.

30 22. An agent for prophylaxis or treatment of diabetic

complications, which contains a compound of the formula



wherein

ring A is an optionally substituted 5 to 10-membered aromatic ring;

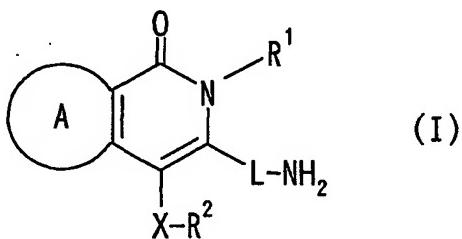
R¹ and R² are the same or different and each is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;

X is a bond, -O-, -S-, -SO-, -SO₂- or -NR³- (R³ is a hydrogen atom or an optionally substituted hydrocarbon group); and

L is a divalent hydrocarbon group, a salt thereof or a prodrug thereof.

15

23. An agent for prophylaxis or treatment of impaired glucose tolerance, which contains a compound of the formula



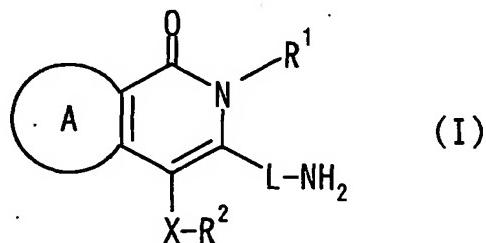
20 wherein

ring A is an optionally substituted 5 to 10-membered aromatic ring;

R¹ and R² are the same or different and each is an optionally substituted hydrocarbon group or

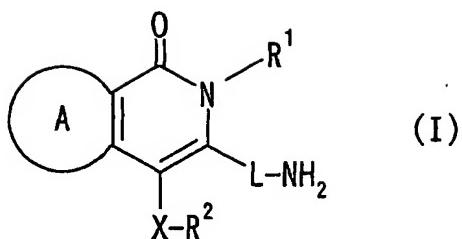
an optionally substituted heterocyclic group;
 X is a bond, -O-, -S-, -SO-, -SO₂- or -NR³- (R³ is a hydrogen atom or an optionally substituted hydrocarbon group); and
 5 L is a divalent hydrocarbon group,
 a salt thereof or a prodrug thereof.

24. An agent for prophylaxis or treatment of obesity,
 10 which contains a compound of the formula



wherein
 ring A is an optionally substituted 5 to 10-membered aromatic ring;
 15 R¹ and R² are the same or different and each is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;
 X is a bond, -O-, -S-, -SO-, -SO₂- or -NR³- (R³ is a hydrogen atom or an optionally substituted hydrocarbon group); and
 20 L is a divalent hydrocarbon group,
 a salt thereof or a prodrug thereof.

25 25. A peptidase inhibitor containing a compound of the formula



wherein

ring A is an optionally substituted 5 to 10-membered aromatic ring;

5 R¹ and R² are the same or different and each is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;

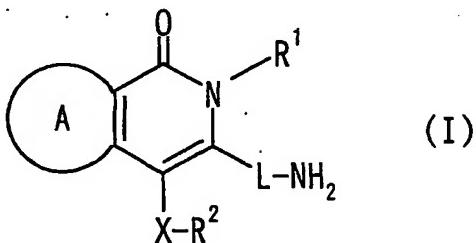
X is a bond, -O-, -S-, -SO-, -SO₂- or -NR³-

10 (R³ is a hydrogen atom or an optionally substituted hydrocarbon group); and

L is a divalent hydrocarbon group,
a salt thereof or a prodrug thereof.

15 26. The inhibitor of claim 25, wherein the peptidase is dipeptidyl dipeptidase IV..

27. A method of prophylaxis or treatment of diabetes in a mammal, which method comprising administering a
20 compound of the formula



wherein

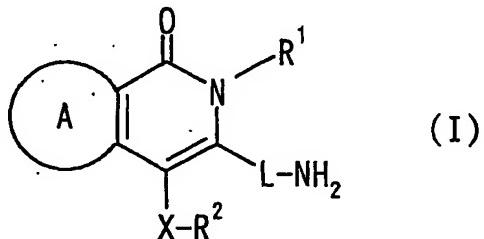
ring A is an optionally substituted 5 to 10-membered aromatic ring;

R^1 and R^2 are the same or different and each is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;

5 X is a bond, $-O-$, $-S-$, $-SO-$, $-SO_2-$ or $-NR^3-$ (R^3 is a hydrogen atom or an optionally substituted hydrocarbon group); and
 L is a divalent hydrocarbon group,
 a salt thereof or a prodrug thereof to the mammal.

10

28. A method of prophylaxis or treatment of diabetic complications in a mammal, which method comprising administering a compound of the formula



15 wherein

ring A is an optionally substituted 5 to 10-membered aromatic ring;

R^1 and R^2 are the same or different and each is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;

20

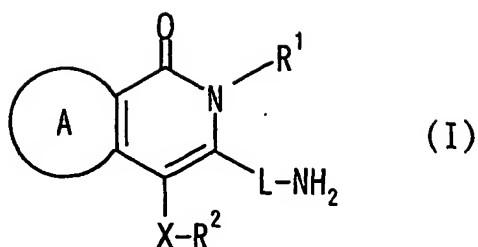
X is a bond, $-O-$, $-S-$, $-SO-$, $-SO_2-$ or $-NR^3-$ (R^3 is a hydrogen atom or an optionally substituted hydrocarbon group); and

25

L is a divalent hydrocarbon group,
 a salt thereof or a prodrug thereof to the mammal.

29. A method of prophylaxis or treatment of impaired glucose tolerance in a mammal, which method comprising

30 administering a compound of the formula



wherein

ring A is an optionally substituted 5 to 10-membered aromatic ring;

5 R¹ and R² are the same or different and each is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;

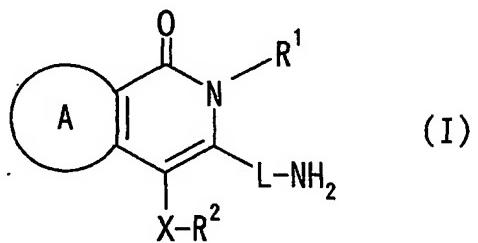
X is a bond, -O-, -S-, -SO-, -SO₂- or -NR³-.

10 (R³ is a hydrogen atom or an optionally substituted hydrocarbon group); and

L is a divalent hydrocarbon group,

a salt thereof or a prodrug thereof to the mammal.

15 30. A method of prophylaxis or treatment of obesity in a mammal, which method comprising administering a compound of the formula



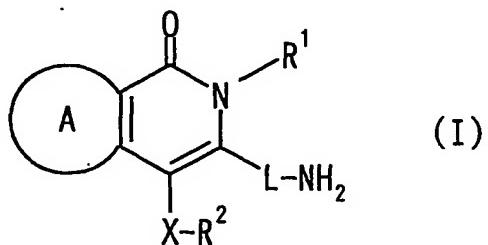
wherein

20 ring A is an optionally substituted 5 to 10-membered aromatic ring;

R¹ and R² are the same or different and each is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic

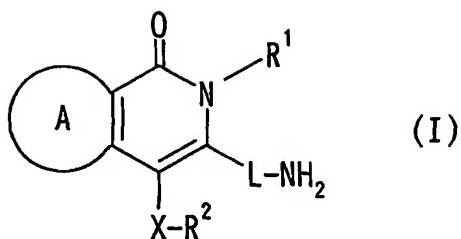
group;
 X is a bond, -O-, -S-, -SO-, -SO₂- or -NR³-
 (R³ is a hydrogen atom or an optionally substituted hydrocarbon group); and
 5 L is a divalent hydrocarbon group,
 a salt thereof or a prodrug thereof to the mammal.

31. A method of inhibiting peptidase in a mammal, which method comprising administering a compound of the
 10 formula



wherein
 ring A is an optionally substituted 5 to 10-membered aromatic ring;
 15 R¹ and R² are the same or different and each is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;
 X is a bond, -O-, -S-, -SO-, -SO₂- or -NR³-
 20 (R³ is a hydrogen atom or an optionally substituted hydrocarbon group); and
 L is a divalent hydrocarbon group,
 a salt thereof or a prodrug thereof to the mammal.

25 32. Use of a compound of the formula



wherein

ring A is an optionally substituted 5 to 10-membered aromatic ring;

5 R¹ and R² are the same or different and each is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;

X is a bond, -O-, -S-, -SO-, -SO₂- or -NR³-

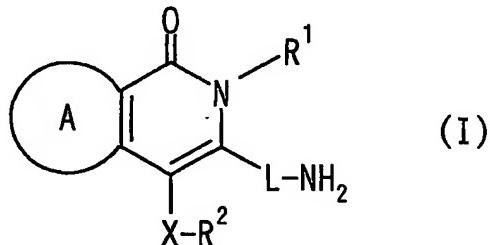
10 (R³ is a hydrogen atom or an optionally substituted hydrocarbon group); and

L is a divalent hydrocarbon group,

a salt thereof or a prodrug thereof for production of an agent for prophylaxis or treatment of diabetes.

15

33. Use of a compound of the formula



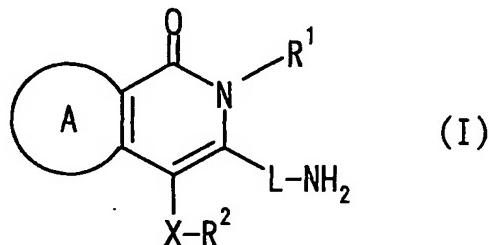
wherein

ring A is an optionally substituted 5 to 10-membered aromatic ring;

20 R¹ and R² are the same or different and each is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;

X is a bond, -O-, -S-, -SO-, -SO₂- or -NR³-
(R³ is a hydrogen atom or an optionally substituted hydrocarbon group); and
L is a divalent hydrocarbon group,
5 a salt thereof or a prodrug thereof for production of an agent for prophylaxis or treatment of diabetic complications.

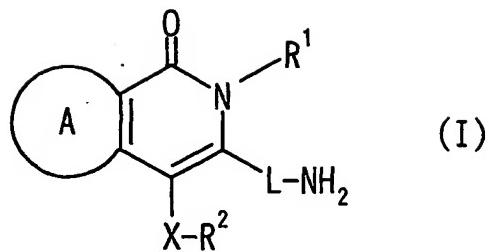
34. Use of a compound of the formula



10 wherein
ring A is an optionally substituted 5 to 10-membered aromatic ring;
R¹ and R² are the same or different and each is an
15 optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;
X is a bond, -O-, -S-, -SO-, -SO₂- or -NR³-
(R³ is a hydrogen atom or an optionally substituted hydrocarbon group); and
20 L is a divalent hydrocarbon group,
a salt thereof or a prodrug thereof for production of an agent for prophylaxis or treatment of impaired glucose tolerance.

25

35. Use of a compound of the formula



wherein

ring A is an optionally substituted 5 to 10-membered aromatic ring;

5 R¹ and R² are the same or different and each is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;

X is a bond, -O-, -S-, -SO-, -SO₂- or -NR³-

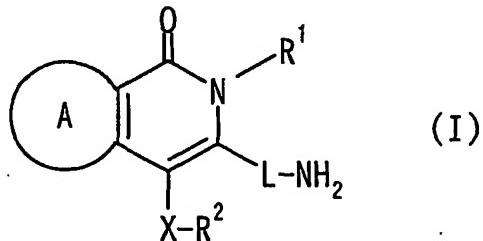
10 (R³ is a hydrogen atom or an optionally substituted hydrocarbon group); and

L is a divalent hydrocarbon group,

a salt thereof or a prodrug thereof for production of an agent for prophylaxis or treatment of obesity.

15

36. Use of a compound of the formula



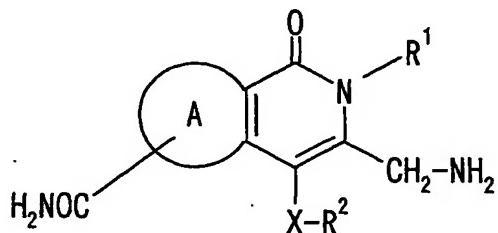
wherein

ring A is an optionally substituted 5 to 10-membered aromatic ring;

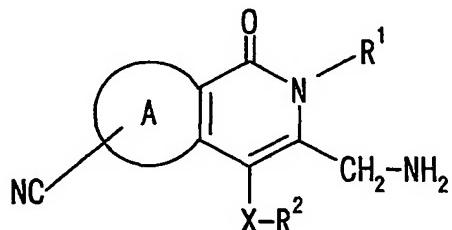
20 R¹ and R² are the same or different and each is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;

- X is a bond, -O-, -S-, -SO-, -SO₂- or -NR³-
 (R³ is a hydrogen atom or an optionally substituted hydrocarbon group); and
 L is a divalent hydrocarbon group,
 5 a salt thereof or a prodrug thereof for production of a peptidase inhibitor.

37. A production method of a compound of the formula

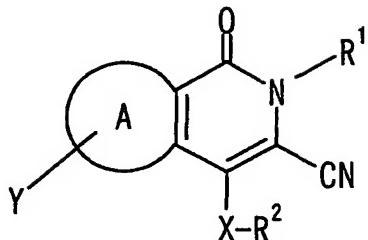


- 10 wherein
 ring A is a 5 to 10-membered aromatic ring;
 R¹ and R² are the same or different and each is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;
 15 and
 X is a bond, -O-, -S-, -SO-, -SO₂- or -NR³-
 (R³ is a hydrogen atom or an optionally substituted hydrocarbon group),
 20 or a salt thereof, which method comprises subjecting a compound of the formula



wherein the symbols are as defined above, or a salt thereof, to hydrolysis.

38. A compound of the formula

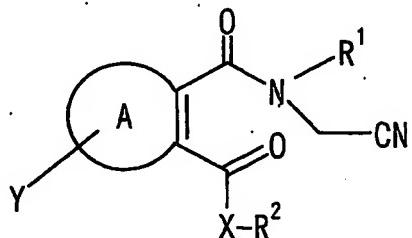


wherein

- 5 ring A is a 5 to 10-membered aromatic ring;
- R¹ and R² are the same or different and each is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;
- 10 X is a bond, -O-, -S-, -SO-, -SO₂- or -NR³- (R³ is a hydrogen atom or an optionally substituted hydrocarbon group); and
- Y is a halogen atom,
or a salt thereof.

15

39. A compound of the formula



wherein

- ring A is a 5 to 10-membered aromatic ring;
- 20 R¹ and R² are the same or different and each is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;
- X is a bond, -O-, -S-, -SO-, -SO₂- or -NR³-

(R³ is a hydrogen atom or an optionally substituted hydrocarbon group); and
Y is a halogen atom,
or a salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 02/00831

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D217/24 A61K31/472 C07D401/12 A61K31/4725 C07D401/06
 C07D417/06 C07D405/06 C07D495/04 A61K31/4365 C07D413/04
 C07D401/04 C07D417/04 //((C07D495/04, 333:00, 221:00))

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

WPI Data, PAJ, CHEM ABS Data, BEILSTEIN Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	K.UNVERFERTH: "Synthese und antikonvulsive Aktivität von 3-Carbamoyl-4-aryl-isochinolin-1(2H)-onen" ARCHIV DER PHARMAZIE, vol. 324, no. 10, 1991, pages 809-814, XP001070958 cited in the application see table 2, 6n,6o,6p and 2->3 and compound 9	38, 39
A	cited in the application see table 2, 6n,6o,6p and 2->3 and compound 9	1-37
X	DD 287 032 A (UNIV LEIPZIG) 14 February 1991 (1991-02-14) see claim 1, formula IV and formula V ----- -/-	38, 39

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the International filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the International filing date but later than the priority date claimed

- "T" later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the International search

10 May 2002

Date of mailing of the international search report

29/05/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Scruton-Evans, I

INTERNATIONAL SEARCH REPORT

National Application No
PCT/JP 02/00831

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 02 24655 A (MERCK & CO INC ;CLAREMON DAVID A (US); LIVERTON NIGEL J (US); MCIN) 28 March 2002 (2002-03-28) see main formula, especially definition of Q and R4,R4' and compounds 33,37,36,29, page 70,39 page 34,114 page 65, 41 page 35 and the compounds 112 and 113 and reaction c, page 42	1-9, 19
Y	EP 0 634 402 A (TAKEDA CHEMICAL INDUSTRIES LTD) 18 January 1995 (1995-01-18) cited in the application see excluded compounds ref examples 4,5 and 6 and also general formula page 19, definitions of W, S-2 and S-5	1-37
Y	IKEURA Y ET AL: "POTENT NK1 RECEPTOR ANTAGONISTS: SYNTHESIS AND ANTAGONISTIC ACTIVITY OF VARIOUS HETEROCYCLES WITH AN N-3,5-BIS(TRIFLUOROMETHYL)BENZYL-N-ME THYLCARBAMOYL SUBSTITUENT" CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN. TOKYO, JP, vol. 45, no. 10, 1997, pages 1642-1652, XP000910111 ISSN: 0009-2363 see compounds 10d,12d	38,39
Y	NATSUGARI H ET AL: "NOVEL, POTENT, AND ORALLY ACTIVE SUBSTANCE P ANTAGONISTS: SYNTHESIS AND ANTAGONIST ACTIVITY OF N-BENZYLCARBOXAMIDE DERIVATIVES OF PYRIDO[3,4-B]PYRIDINE" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 38, 1995, pages 3106-3120, XP002925569 ISSN: 0022-2623 see compounds 8,9	38,39
A	WO 98 38168 A (TANABE SEIYAKU CO ;IKEO TOMIHIRO (JP); OMORI KENJI (JP); UKITA TAT) 3 September 1998 (1998-09-03) the whole document	1-37
A	EP 0 585 913 A (TAKEDA CHEMICAL INDUSTRIES LTD) 9 March 1994 (1994-03-09) see also page 39, compounds XV,XVI the whole document	1-39
A	WO 98 18763 A (ASAI YASUYUKI;TANABE SEIYAKU CO ; OHNUKI TETSUO (JP); TANAKA SUMIK) 7 May 1998 (1998-05-07) the whole document	1-39

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/JP 02/0083

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WO 0224655	A	28-03-2002	WO	0224655 A1	28-03-2002
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WO 9838168	A	03-09-1998	AU JP WO	6230098 A 10298164 A 9838168 A1	18-09-1998 10-11-1998 03-09-1998
EP 0585913	A	09-03-1994	AT AU AU CA CN DE DE EP FI HU JP NO NZ US US	161530 T 667739 B2 4613293 A 2105518 A1 1090274 A 69315920 D1 69315920 T2 0585913 A2 933857 A 67284 A2 7010844 A 933133 A ,B, 248583 A 5482967 A 5700810 A	15-01-1998 04-04-1996 10-03-1994 05-03-1994 03-08-1994 05-02-1998 10-06-1998 09-03-1994 17-05-1994 28-03-1995 13-01-1995 07-03-1994 27-04-1995 09-01-1996 23-12-1997
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 02/00831

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6 090 786 A (BORLOO MARIANNE JEAN FRIEDA ET AL) 18 July 2000 (2000-07-18) see Table 1, line 27 the whole document	1-37